HEPATIC DYSFUNCTION IN CHILDREN WITH DENGUE VIRAL INFECTION IN PSG HOSPITALS

Dissertation Submitted to

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

In fulfilment of the regulations for the award of the degree

M.D. (PAEDIATRICS)

DR.KICHU GEORGE

POST GRADUATE STUDENT

DEPARTMENT OF PAEDIATRICS

PSG INSTITUTE OF MEDICAL SCIENCE AND RESEARCH

PEELAMEDU, COIMBATORE -641 004

APRIL 2013

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GUIDE

DR.JOHN MATTHAI, DCH, MD

PROFESSOR AND HOD, PEADIATRICS

APRIL 2013

CERTIFICATE

This is to certify that the thesis entitled "**HEPATIC DYSFUNCTION IN CHILDREN WITH DENGUE VIRAL INFECTION IN PSG HOSPITALS"** is the bonafide work of Dr. KICHU GEORGE done in the department of Paediatrics , PSG Institute of Medical Sciences and Research, Coimbatore under the supervision of Dr.JOHN MATTHAI, Professor and head of Paediatrics in fulfilment of the regulations of the Tamil Nadu Dr.MGR Medical university for the award of MD degree in Paediatrics

DR.RAMALINGAM

PRINCIPAL

PSG IMS&R

DECLARATION

I hereby declare that this dissertation "**HEPATIC DYSFUNCTION IN CHILDREN WITH DENGUE VIRAL INFECTION IN PSG HOSPITALS"** is my bonafide work and prepared by me under and supervision of DR.JOHN MATTHAI, Professor and head of Paediatrics, PSG Institute of Medical Sciences and Research, Coimbatore.

The dissertation is submitted to The Tamil Nadu Dr.MGR Medical University in fulfilment of the University regulation for the award of MD degree in Paediatrics. This dissertation has not been submitted for the award of any other Degree or Diploma in this for any other University.

DR.KICHU GEORGE

CERTIFICATE BY THE GUIDE

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DR.JOHN MATTHAI

PROFESSOR AND HEAD OF PAEDIATRICS

PSG IMS&R, COIMBATORE

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Contents

MASTER CHARTS KEY WORDS

A	- AGE
S	- SEX
SG	- SGPT
LP	- LOWEST PLATELET VALUE
PT	- PROTHROMBIN TIME
AP	- ACTIVATED PARTIAL PROTHROMBIN TIME
LS	- LIVER SPAN
T	- TRANSFUSIONS
R	- REPEAT SGPT
T	- TYPE OF DENGUE
C	- COMPLICATIONS
D	- DURATION OF HOSPITAL STAY
PS	- PICU STAY
P	- PLATELET
F	-FRESH FROZEN PLASMA

Introduction

Dengue fever (DF) is endemic in many South East Asian countries. It is caused by one of the four types of dengue virus, which is spread by Aedes aegypti mosquito. An estimated 2.5 to 3 billion people are at risk of acquiring this illness worldwide. Five lakhs of DHF require hospitilization each year, of which 90% are children, less than 15 age. The recent major epidemics in South East Asia regions occurred in India, Sri Lanka, Thailand, Myanmar and Indonesia. The number of cases have increased over the last 3-5 years with recurring epidemics and increasing incidence of DHF and DSS(1). The factors implicated for the increasing incidence in these epidemics are not fully understood. Unprecedented global population growth and unplanned urbanization in tropical countries has been the root cause for the spread of these epidemics. This has lead to poor housing standards, overcrowding and deterioration of water, sewer and waste management systems. There has also been increase in the air travel providing the ideal mechanism for spread of the virus across the major continents.

Broadly, the management of these cases involves segregating them into those with the milder forms of disease, dengue fever from dengue hemorrhagic fever, which may progress rapidly to shock, multiorgan dysfunction and death. Recognition of capillary leak, which forms the defining factor for the serious form of this infection, becomes very important in the

management of these cases. If untreated, mortality from the complications of DF is as high as 20% whereas if recognized early and managed properly, mortality is less than 1%.

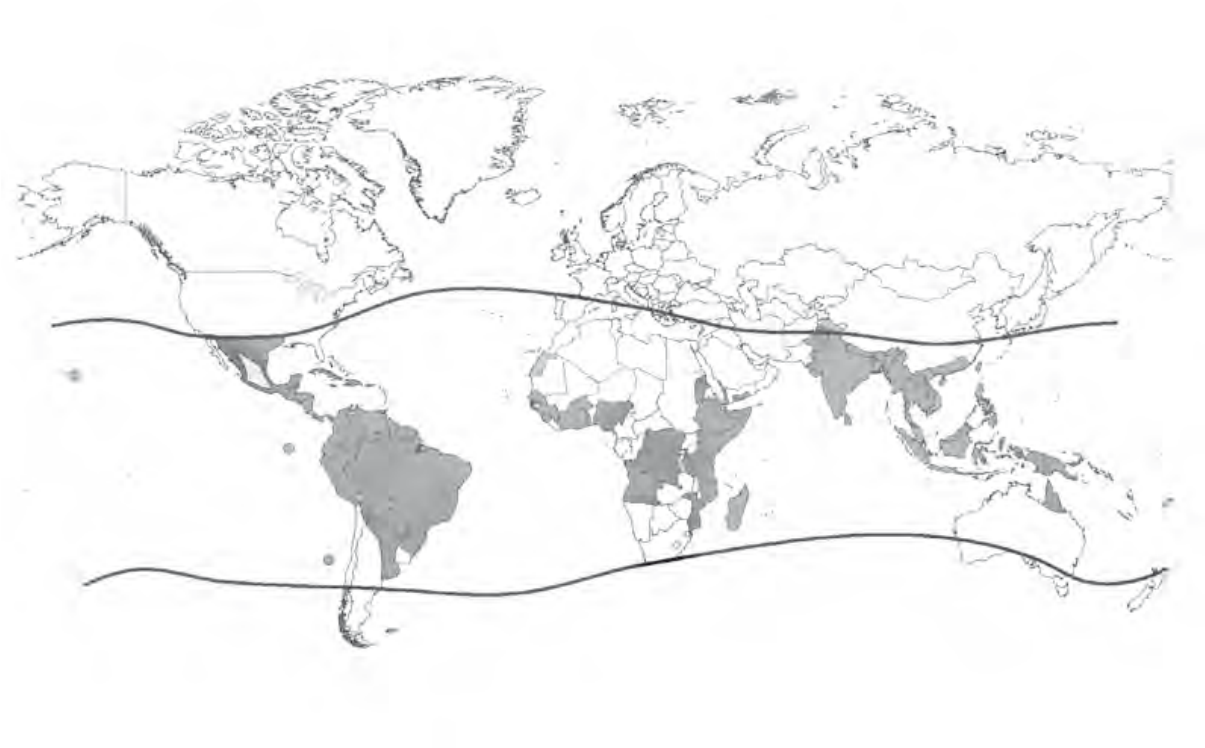
The present study analyses the frequency and degree of hepatic dysfunction in children < 15yrs admitted with dengue infection. The severity of liver dysfunction in affected children by DI varies from mild injury with mild elevation of transaminases activity to very severe injury presenting with jaundice [32-34]

REVIEW OF LITERATURE

Dengue infection is the most common mosquito –borne viral disease of humans that it has become a major international public health care in recent years. The incidence has increased 30 fold in last 50yrs, geographically expanding to other countries as shown in the fig 1.1[1].

Figure 1.1 Countries/areas at risk of dengue transmission, 2008

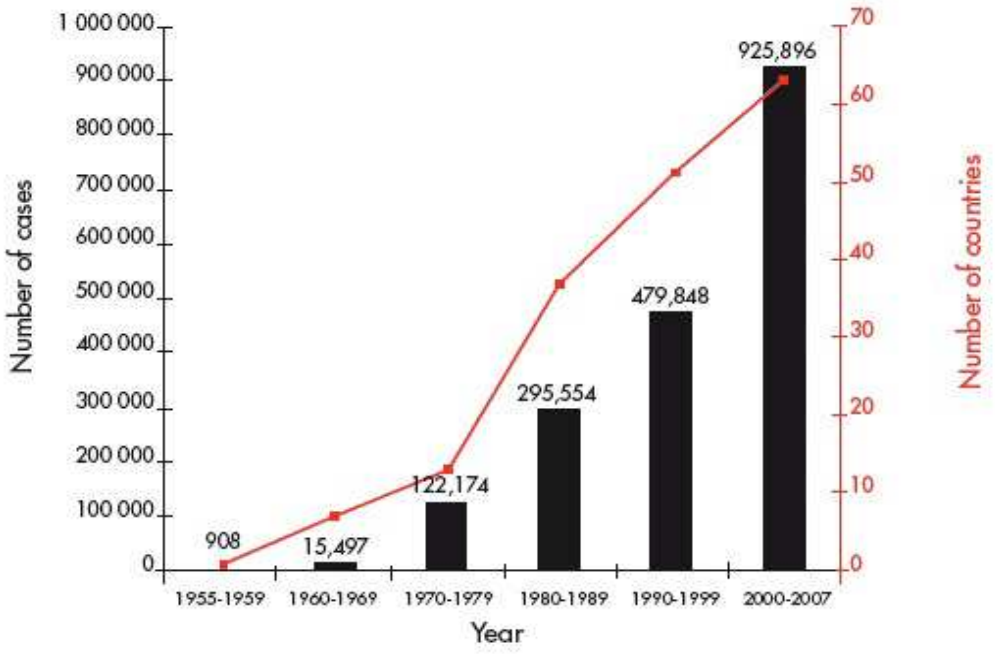
Data Source: World Health Organization Map
Production: Public Health Infrmation and Geographic
Information Systems (GIS) World Health Organization
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines or maps represent approximate border lines for which



Around 50 million dengue infections occur every year and approximately 2.5 billion people live in dengue endemic countries [(1)]. The global incidence of dengue has increased abruptly in recent decades [(1, 2).] In 1905 Bancroft identified the vector for dengue as aedes aegypti [(3)]. The isolation of dengue virus type 1 & 2 in 1943 and 1944 marked the modern era of dengue research. The

etiological agent for dengue was found in human blood by Craig and Askburn [4].Many epidemics have been reported since virus was isolated in 1945 [5, 6, 7, 8, 9, 10]. Dengue infection is an endemic in more than 100 countries in Africa, America, Southeast Asia, West pacific and Eastern Mediterranean. Nearly > 70% population worldwide at risk of dengue, live in member states of WHO, Western pacific region and South East Asia region bearing nearly 75% global burden of the disease[1]. The first epidemic was recorded in the Chinese encyclopaedia of diseases, symptoms, and remedies written during Chin dynasty (265- 420 AD), edited in 610 AD (Tang dynasty) and in 992 AD (Northern sung dynasty). The Chinese first called the disease as water poison and thought it was spread by flying insects [11]. In Manila it was called Philippine hemorrhagic fever in 1954 [12].By 1970, 9 countries had experienced dengue epidemics. Since 2000, epidemic has spread to new areas and in 2003, 8 countries reported dengue cases [1]. In 2005 WHO's Global Outbreak Alert and Response Network (GOARN) responded to an outbreak in Timor –Leste with a high case fatality rate [1]. The number of dengue infections reported to WHO up to 2007 is shown in fig 1.2

Figure 1.2 Average annual number of dengue fever (DF) and dengue haemorrhagic fever (DHF) cases reported to WHO, and of countries reporting dengue, 1955–2007



Nearly 5, 00,000 people with dengue fever require hospitalisation every year majority being children. Nearly 2.5% of them die without proper treatment. Proper treatment at the appropriate time can reduce death rates to < 1%.

Dengue in our country

First case of dengue fever was reported from Vellore district (Tamil Nadu) in 1956. Calcutta in West Bengal reported the first DHF during an outbreak with 30% cases showing hemorrhagic manifestations. All the 4 serotypes of dengue -1, 2, 3, 4 have been isolated in India. The major outbreak in Delhi was in 1988 and then in 1996 [5, 6, 13, 14]. Dengue cases have been on the rise since 1997 in Tamil Nadu [15]. An epidemic was reported from Chennai

during September 2001 & 2002 with majority of the children being less than 5 years [16, 17].

Dengue virus

Dengue virus (DEN) is a small single stranded RNA virus with four different serotypes (DEN 1-4) belonging to genus Flavi virus and family Flaviviridea [1]. The Flavi virus is small with a lipid envelope and is spherical in shape. Though all 4 serotypes are antigenically similar; they differ to elicit cross protection only for a few months. Infection with one dengue serotype gives life long immunity to that virus serotype only.

The Vectors

The DEN virus is transmitted to humans only when an infected Aedes aegypti takes a blood meal. They are seen in both tropical and subtropical areas widely distributed mostly between latitudes 35° N and 35° S [1]. They are not seen in high altitudes. The female mosquito lays eggs on damp surfaces above water line. Under optimal conditions the aquatic stage can be as short as 7 days. The eggs can survive without water for 1 year. The adult survival is an average of 15 days. Their survival is longer during rainy season and the risk of virus transmission is greater. They are typically daytime feeders and have to feed on many people to complete one full meal there by infecting them all.

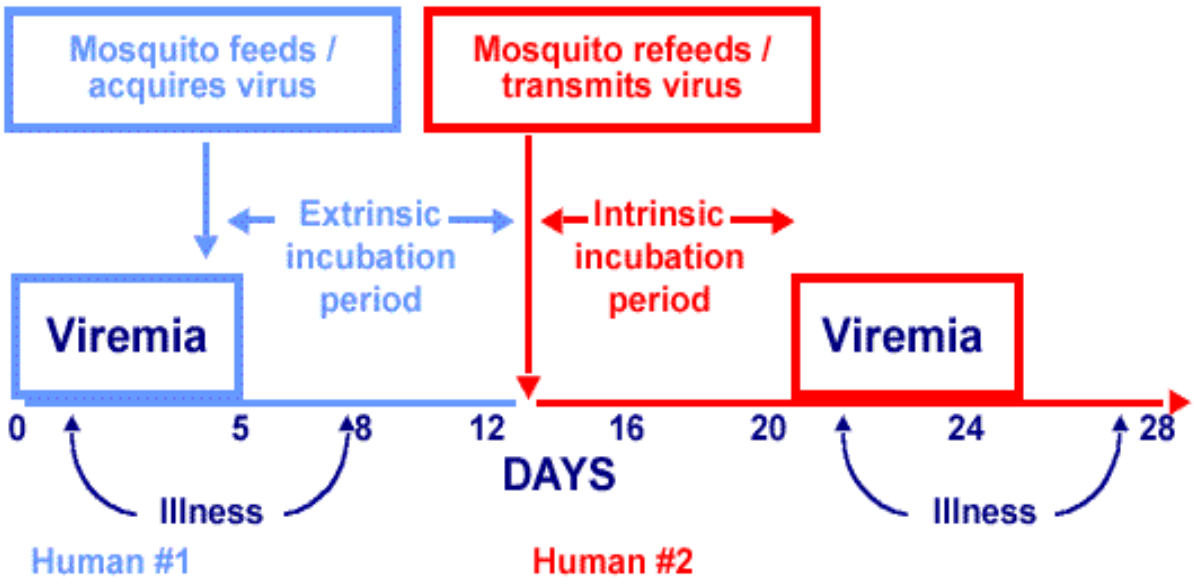
The Host

Infection by any of the 4 serotypes after an incubation period of 4-10 days produce wide spectrum of illness though most infections are asymptomatic or subclinical (1). Travel to dengue epidemic area is an important risk factor. Individual risk factors like age, secondary infection, ethnicity and possibly chronic diseases determine the severity of disease. Young children are at greater risk of dengue shock because their ability to compensate for capillary leakage is much less when compared to adults.

Environmental factors

The mosquito's life span is influenced by temperature and humidity. They survive best between a temperature of 16 – 30 degrees and a relative humidity of 60 -80%. Rainfall and water storage influences their population.

Transmission cycle [18, 19, 20]



Aedes aegypti gets infected with the dengue virus when the female species of the mosquito takes a blood meal from a person in his acute febrile phase of illness (viremia). After 8 to 10 days which is the incubation period, the mosquito gets infected and transmits the dengue virus into the next person while taking a blood meal. There is also evidence of trans ovarian transmission where there is evidence of vertical transmission from infected mosquitoes to the eggs.

Maximum blood meals are taken during early morning and in afternoons. For one complete meal a female Ae. aegypti feeds on several people infecting them all. After a person has been bitten the virus has an incubation period of 4 to 7 days following which the infected person develops acute onset of fever along with many non-specific signs and symptoms [21]. The infected dengue virus will continue to circulate in the peripheral blood [22].When another female mosquito takes the meal from the infected person during his viraemic stage, that mosquito also gets infected and thereby transmits virus to another uninfected person after an incubation period of 8 to 10 days [16, 18].

Pathophysiology and pathogenesis

Pathogenesis of DHF is not fully understood but 2 Patho physiological changes suggested are [1]

a) Increased vascular permeability resulting in plasma leakage, hypovolemia and shock and

b) Abnormal haemostasis due to vasculopathy , thrombocytopenia and coagulopathy leading to various hemorrhagic manifestations .The causes for the above changes are not clear.

Two theories put forth are [11]:

Immune enhancement hypothesis - says that patients with a secondary DI with a heterologous DEN serotype have increased risk of developing severe dengue.

The 2nd hypothesis says that DEN virus vary and change genetically like all animal viruses where increased virus replication and viraemia are the forms of phenotypic expression.

Differential diagnosis of dengue fever

Chicken gunya

Rubella

Coxsackie infections

Infectious mononucleosis

Influenza

Leptospirosis

Rickettsial infections

Differential diagnosis of severe dengue

Chicken gunya

DIC with gram negative sepsis

Kawasaki disease

Leptospirosis

Meningococcal sepsis

Classification of dengue

Dengue fever

Dengue fever can occur in both primary and secondary infections. The onset is abrupt with high grade fever along with other features like abdominal discomfort, myalgia, arthralgia, anorexia, severe headache and occasionally maculopapular rash. The fever pattern is usually biphasic and lasts 2 to 7 days[23]. Coryza and flushed appearance are the other commonly observed features in young children whereas vomiting, headache and abdominal are less commonly seen. Bleeding manifestations are minimal in dengue fever though purpura, epistaxis, petechiae and gingival bleeding have been reported in some individuals [24]. Complications in dengue fever are very minimal and most of them recover uneventfully.

Dengue haemorrhagic fever

DHF is usually seen in secondary dengue infections but can also occur in primary infections especially in infants. The fever pattern then again is similar to dengue fever lasting for 2 to 7 days. Once the temperature drops to normal levels the patient may either completely recover or develop plasma leakage. Those children who remain sick after the fever crashes are the ones who have a high chance of developing DHF. In those children with DHF defervescence usually occurs between day 3 and 4 [25]. Plasma leakage sets in within 24 to 48hrs after the onset of DHF with clinical signs of hypotension and tachycardia. Severe plasma leakage results in circulatory disturbances like narrow pulse pressure prolonged capillary refill time and may even cause shock.

Ascites and pleural effusion are the other common manifestations of plasma leakage. Very rarely has pericardial effusion been reported and is associated with high morbidity and mortality. Bleeding manifestations are usually seen once the fever has subsided [26]. The most common site of bleeding is the GI tract and is usually manifested in the form of hematemesis or malena. The recovery is usually fast and return of appetite is a good sign of recovery.

Dengue shock syndrome

DSS is the most severe form of dengue infection and has a very high mortality rate. There is often severe plasma leakage resulting in circulatory disturbances, circumoral cyanosis and cold peripheries. Persistent vomiting and acute abdominal pain are the early danger signs of impending shock. Sudden fall in blood pressure may indicate a profound shock[27]. Profound shock may result in metabolic acidosis which could precipitate disseminated intravascular coagulation resulting in massive bleeding. DSS could result in dengue encephalopathy which could be triggered either by metabolic or electrolyte disturbances.

Case definition

Dengue fever - Fever usually lasts 2 to 7 days and has 2 or more of the following feature:

Headache

Rash

Bleeding manifestations

Leukopenia

Myalgia or arthralgia

Dengue hemorrhagic fever- Criteria includes a serologically confirmed dengue infection with one or more of following hemorrhagic tendencies:

Positive tourniquet test

Petechiae, ecchymoses or purpuric spots

Platelet value less than 1, 00,000

Newer classification

1. Dengue fever:

Live in/ travel to endemic area,

Fever + 2 of following criteria:

Nausea, vomiting, rash, aches and pain positive tourniquet test,thrombocytopenia < 1 lakh and any warning signs .

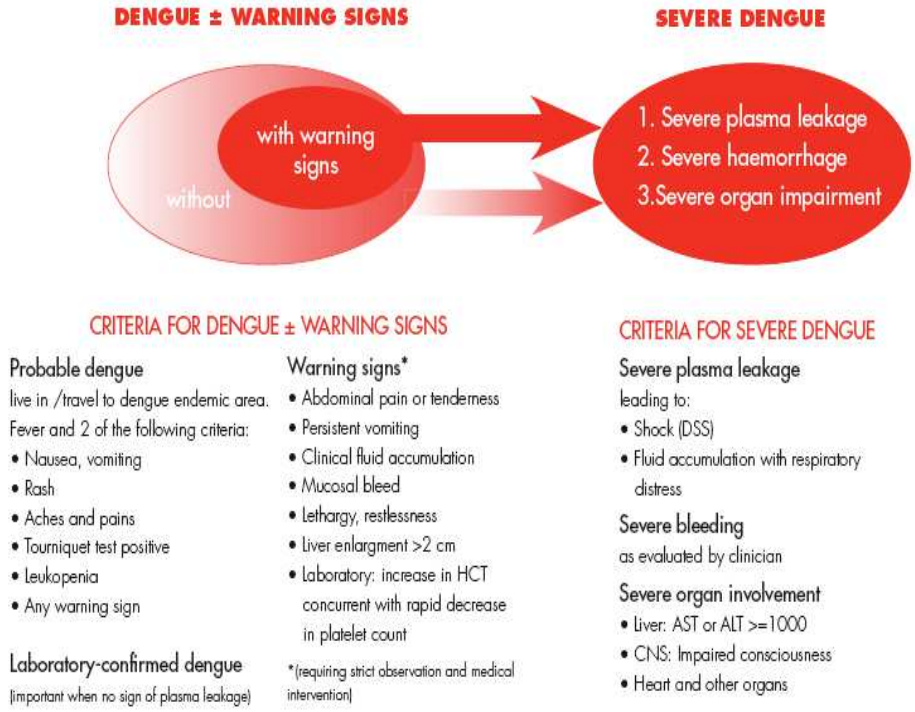
The warning signs are: Abdominal pain / tenderness, Persistent vomiting, Clinical fluid accumulation, mucosal bleed, Lethargy, restlessness, Liver > 2 cm palpable, Increase in hematocrit with rapid fall in platelet.

2. Severe dengue

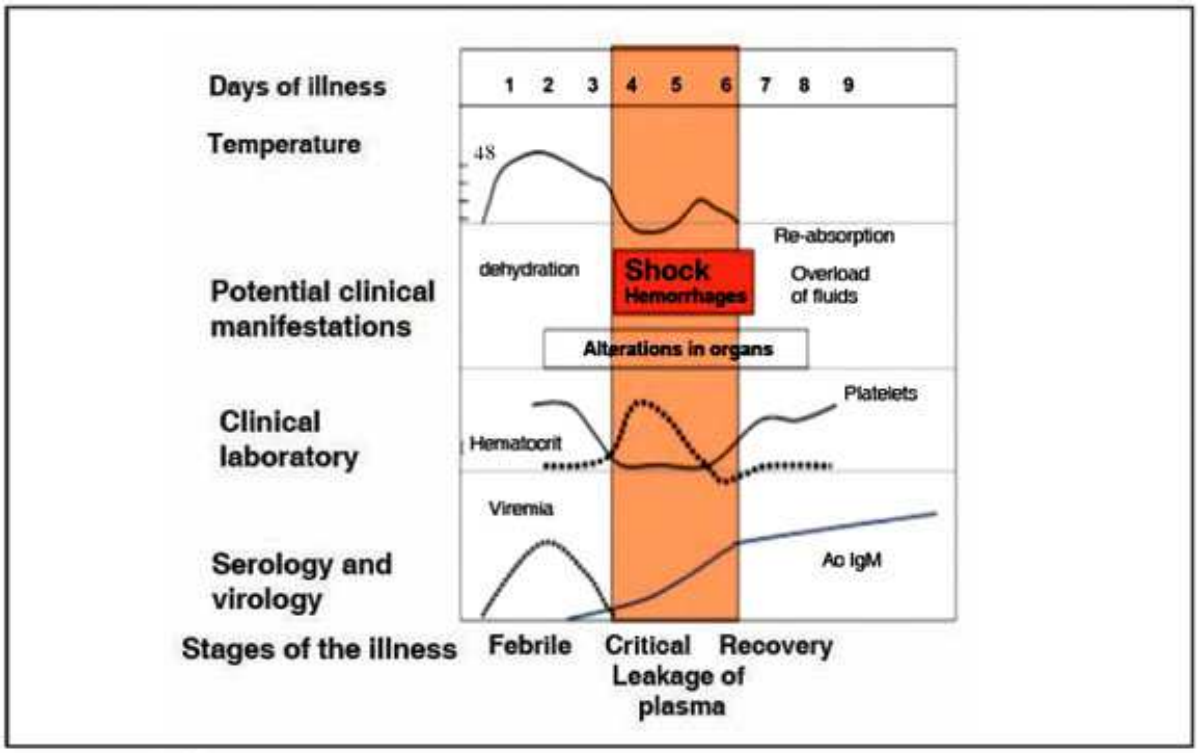
Severe plasma leakage leading to shock, fluid accumulation with respiratory distress

Severe bleeding

Severe organ involvement - increased SGPT / SGOT, impaired consciousness



Course of dengue illness



Source: Formulated by Eric M. Torres.

Figure 2 – Progress of the dengue illness.

Febrile phase

Develops high grade fever suddenly **,**Lasts 2- 7 days accompanied by facial flushing , skin erythematic , generalized body aches , myalgia , arthralgia and headache. Anorexia, nausea and vomiting are common**.** Positive tourniquet test increases possibility. Petechiea and mucosal bleeds may be seen. Massive vaginal bleed/ GI bleed may occur but not common .Liver is often enlarged and tender.

Critical phase

Around time of defervescence, temperature drops to normal or less; usually 3 – 7 days of illness.

There is increase in capillary permeability in parallel with a increase in hematocrit.

Clinically significant plasma leakage lasts 24 – 48 hours.

Progressive leucopenia followed by decrease in platelet count usually precedes plasma leakage.

Patients without an increase in capillary permeability will improve while those with become worse as a result of lost plasma volume.

Degree of increase in hematocrit above baseline reflects severity of plasma leakage.

Pleural effusion and ascites occurs depending on degree of plasma leakage and volume of fluid therapy.

Shock occurs when critical volume of plasma is lost through leakage.

Prolonged shock results in organ impairment, metabolic acidosis and DIC leading to severe hemorrhage causing hematocrit to decrease in severe shock.

Recovery phase

After 24 – 48 hrs of critical phase; gradual re -absorption of extra vascular compartment takes place in following 48 – 72 hrs

Features:

General well being improves

Appetite improves

GIT symptoms abate

Hemodynamic status stabilizes and diuresis ensues

Bradycardia

Some experience generalised pruritis

PCV stabilizes

Leucopenia starts to rise

Platelet count increases

Respiratory distress from massive pleural effusion or ascites will occur if excessive fluid is administered.

Laboratory diagnosis

Criteria for laboratory diagnosis: one or more of the conditions below

The virus should be isolated from plasma, serum, leucocytes or autopsy sample.

Four fold or higher rise in reciprocal IgG or IgM antibody titres to one or more of the dengue viral antigens.

Dengue viral antigens demonstrated in serum samples by ELISA or in autopsy tissue by immune histochemistry.

Dengue viral genomic sequence detected by PCR in autopsy tissue and serum sample.

The gold standard for diagnosis of dengue infection is isolation of the virus and the second best alternative is to confirm by serology. The serological tests available are:

Hemagglutination test (HI)

Compliment fixation test and neutralization test

MAC ELISA IgM immunosorbent assay and indirect IgG ELISA

SEROLOGICAL DIAGNOSIS

IGM ELISA

The test is based on detecting dengue specific IgM antibodies in the serum and to capture them using anti-human IgM. This is a very simple rapid test and requires very minimal sophistication. For easy detection an enzyme substrate is added to give colour to the reaction. 80% of patients in primary dengue infection show IgM antibodies by day 5 and 99% within 20days. The IgM antibodies peak at 2wks and come down over the next 2 to 3 months. In secondary dengue IgM response is low and slow and some patients might not even show detectable IgM.

IgG ELISA

Primary dengue infection can be distinguished from secondary dengue using an indirect IgG ELISA by comparing with IgM. This test is non-specific and shows same broad cross reactivity among Flavi virus and cannot be used to identify the dengue serotype. In primary dengue IgG rise later and gradually decline to lower level which persists for life. In secondary dengue infection the IgG response is rapid and is much higher when compared to the response in primary dengue. The IgG value peaks at 2 weeks and slowly comes down over 3 to 6 months.

The IgG and IgG serology is relatively inexpensive and is simple to perform[33]. The test has good sensitivity and can be done real quickly. The IgM ELISA has a sensitivity of 84% -98.5% and a hundred percent specificity[39]. Ideally both the serological tests should be performed during the acute as well as convalescent period but for cost reasons and difficulty of revisit, only one sample is sent after 5 days of illness.

Other tests available

Hemagglutination inhibition test (HI) test

In the past this was the most widely used method for serological diagnosis. The limitations of this method were extensive cross-reactions, time consuming and need for repeated samples during both acute and convalescence period.

Compliment fixation test

This test is not routinely done nowadays .This test requires highly trained people and reagents which are thermolabile which makes it all the more difficult.

Rapid diagnostic test [44, 45, 46]

A lot of commercial kits for rapid diagnosis are available in the market. Though we get the results within 15 to 20 mins, WHO GUIDELINES have not recommended this test to guide management of dengue.

PCR technique [47, 48]

In dengue PCR gives a rapid and serotype specific diagnosis. This test is simple, sensitive and reproducible if well controlled.

Management:

3 groups

Group A – These patients can be sent home, these patients are able to take adequate oral feeds, pass urine at least once in 6hrs and have no warning signs.

GROUP B – they require in hospital management. These are patients with warning signs.

Obtain an urgent hematocrit and start isotonic solutions such as 0.9% saline, RL or Hartmann's solution.

Start with 5- 7 ml/kg/hr for 1- 2 hrs

↓

Reduce to 3- 5 ml/kg/hr for 2 – 4hrs

↓

Decrease to 2 – 3 ml/kg/hr or less

Reassess the clinical status and repeat hematocrit value. If hematocrit remains same or rises only minimally; continue with same rate of fluids [2- 3 ml/kg/hr].If vital signs are worsening and hematocrit value is rising rapidly , increase rate to 5 – 10 ml/kg/hr for 1-2hrs.Reassess clinical status and repeat hematocrit value and review fluid infusions accordingly .Continue with minimum fluids to maintain good perfusion and urine output.Iv fluids are needed only for 24-48hrs.Decrease the rate of fluids when plasma leakage decreases towards end of critical phase .

Group c

In cases of severe plasma leakage leading to shock / fluid accumulation with respiratory distress, Severe hemorrhages, Severe organ impairment [hepatic damage, renal impairment, cardiomyopathy , encephalopathy / encephalitis].

The goals of treatment should be: Improving central and peripheral circulation, decreasing tachycardia , improving BP & pulse volume, warm and pink extremities, CRT < 2 sec, Improving end organ perfusion, stable conscious levels and to maintain an urine output more than or equal to 1ml/kg/hr.

Hepatic dysfunction in dengue

Liver involvement is seen in children with dengue [28-30]. Dengue virus though not a hepatotoxic virus, many cases of liver injury due to DI has been described since 1960 [31]. The severity of liver dysfunction in affected children by DI varies from mild injury with mild elevation of transaminases activity to very severe injury presenting with jaundice [32-34]. A direct viral effect or a consequence of deregulated host immune response against the virus could be the reason for liver dysfunction [35]. Pathological changes in the portal tract like centrilobar necrosis, fatty changes and monocyte infiltrations have been reported[36].Varying abnormalities of liver enzymes are seen in symptomatic dengue patients but their recovery is also soon (Pancharoen et al 2002).Severity of liver dysfunction depends on the type of DI and is more common in patients with severe dengue. Even in children the ones with severe dengue has been reported to have profound liver involvement [28,37].Recent Studies from Thailand and India shows that the most important cause of acute hepatic failure in children is DI contributing to 34.3% and 18.5% [38,39].

The hepatic dysfunction in DI is shown to have a close association with the severity of the disease. Higher levels of liver injury are a good positive predictive factor for development of severe dengue [40]. Studies have shown that there is more than a 10 fold rise in transaminases of children when compared to adults [41, 42]; this clearly states that children are at higher risk of liver injury than

adults. Study done in Lady Hardinge medical college, New Delhi of 61 children showed that SGPT and SGOT were elevated in 80 – 87%. A similar study in JSS medical college, Mysore showed that 17.27 % of children had more than 10 fold rises in transaminases levels .The SGPT values were elevated in 69.4 % of patients with dengue fever and 92% with severe dengue. There were 82.2% of children who had elevated levels of SGPT in a study of 270 patients done by Kuo et al in 1992. Mohan et al in 2000 studied 61 children in which 96% had elevated SGPT levels in the severe dengue group. During an epidemic in Brazil in 2004 Souza et al found that 45% of the cases in a study group of 1585 were found to have a higher SGPT levels.

The patho physiology of liver injury in DI is not clear. Few mechanisms suggested were [(43)]. 1) Host immune response system killing virus infected cells. 2) The virus having a direct cytopathic effect. 3) Shock and hypotension having a non specific effect. Gholson et al in 1990 in his Studies showed that SGOT levels are much more elevated than SGPT levels .The reason suggested was due to excessive release of SGOT from damaged monocytes during DI (Chung et al; 1992). Since SGOT has a shorter life span of 12.5-22h when compared to SGPT which has a life span of 32-43 hrs; the raised SGOT levels normalise much faster than the SGPT levels.(hawker 1991)

There are a few authors who suggested that drugs like acetaminophen and anti emetics taken during the febrile phase potentiate the liver damage (Suvatte et al 1990).

Though liver size has no connection whatsoever with the severity of disease; hepatomegaly is more frequently seen in children in shock when compared to non-shock cases [44]. Study in JSS medical college reported 79% of 110 cases with hepatomegaly. Faridi and Petdachai et al had reported 100% hepatomegaly in their study group. Isolation of the dengue virus from the liver has been done in fatal cases. Similar findings were seen by Burke et al in 1968, Sumarmo et al in 1983 and by Rosen et al in 1989. Huerre et al , Rosen et al and Bhamarapravati et al found liver to be the main organ where the dengue virus was isolated. Using immunohistochemistry, in situ PCR technique and in situ hybridization, dengue virus antigens and nucleic acid has been recovered from liver tissue though no studies have shown whether viral multiplication happens in hepatocytes or not [45- 47].Contradicting this Huerre et al in 2004 says that DEN virus replicates in Kupffer cells and hepatocytes. Marianneau et al says though the DEN enters Kupffer cells effectively, their replicate infective capacity is not very efficient. Rosen et al says in his study that DEN 2 or 3 were isolated in 5 out of 17 cases using mosquito inoculation technique. Studies have shown that specific CD4+ and CD8+ T cells play a major role in the pathogenesis of severe dengue forms.

SERUM GLUTAMIC PYRUVIC TRANSAMINASE:

It is also known as Alanine transaminase is an enzyme that when elevated suggests hepatocellular injury or inflammation.

It also occurs in small amounts in cardiac muscle, skeletal muscle and in kidney but is much more specific to the liver than aspartate transaminase.

The most marked rises of both alanine transaminase and aspartate transaminase levels may occur with acute hepatocellular injury.

SGPT is elevated in any hepatitis (A,B,C) , toxin exposure , medications (anticonvulsants , Isotretinoin , rantidine, cimetidine, isoniazid and statins),non-alcoholic fatty liver disease and blunt trauma.

Normal range varies from laboratory to laboratory and we considered taking 10 – 40 IU/L as normal value according to our lab.

PROTHROMBIN TIME

It measures the activation of clotting by tissue factor in presence of calcium.

It is elevated in conditions with deficiency of clotting factors involved in extrinsic pathway and deficiency of vitamin K due to intestinal malabsorption (cholestasis) or due to intake of vitamin K.

Normal Prothrombin time is 10 to 13 seconds.

Prothrombin time has been standardized using the International normalised ratio (INR) so that values can be compared from one laboratory or instrument to another.

This ratio is used to determine similar degree of anticoagulation with warfarin like medications.

Activated partial thromboplastin time:

It measures the intrinsic pathway.

The measurement of partial thromboplastin time as performed in lab is actually “activated” partial thromboplastin time. This test measures the initiation of clotting at the level of factor XII through sequential steps to the final clot end point.

It does not measure factor VII, factor XIII or anticoagulants.

PTT uses a contact activator (silica, kaolin, or ellagic acid) in the presence of calcium and phospholipid. Because of the differences in the reagents & lab instruments normal range for PTT varies between one hospital laboratory and another.

Normal ranges of PTT are much more variable from lab to lab than in the case of PT.

Our lab normal value is from 24 to 35 seconds.

Aim

To asses the frequency and degree of hepatic dysfunction in children less 15yrs admitted with dengue infection as patients in PSG hospitals.

Materials and Methods

Type of study : Prospective cohort study

Place of study : PSG Institute of Medical Sciences And Research, Coimbatore.

Study population : Children in age group > 0 – 15 yrs

Both Sexes

Only children with serologically proven Dengue infection were included.

Period of study : 1 year (July 2011 – July 2012)

Inclusion criteria

All children who were admitted with serologically proven Dengue infection between the age group 0 – 15yrs were included in the study.

Exclusion criteria

Chidren with history of chronic liver disease.

Those who are on hepatotoxic drugs.

Children with pre-existing chronic infections.

Children who are potential hepatotoxins.

Method

All children between the age group 0-15 years admitted for clinically suspecting dengue infection and later serologically proven dengue (ELISA IgG and IgM) were included in the study. The study period was between One year (July 2011 – July 2012) and 136 consecutive samples were included in the study based on inclusion criteria. Informed consent was obtained and detailed history taken from the parents. Ethical committee approval from PSG Hospitals was obtained. All the 136 children underwent investigations according to the hospital's dengue protocol and requirement of the study. The investigations done were complete blood count showing total and differential count, haemoglobin, hematocrit, platelet and ESR values. Other investigations done were SGPT, PT, APTT, dengue serology and chest X ray based on the clinical picture. Dengue serology was done on the 7^{th} day after onset of disease. Platelet and SGPT values were repeated on a regular basis during the hospital stay depending on the clinical status of the patient. From all the serologically proven dengue cases with elevated ALT levels, blood samples were obtained to rule out other causes of liver injury. Hepatitis A, B and E were ruled out from all the 136 children included in the study. Ceruloplasmin levels could not be done because of the financial limitation of the study. Management of the children were left to the respective treating units. Children with elevated SGPT values at discharge were asked to repeat the test at 2 weeks.

For comparison purposes the total of 136 children were divided into 3 groups based on their ALT value. The first group was the group with a normal ALT values (SGPT<40IU/L). The second group was the 2 with slightly elevated ALT values (ALT between 40-100IU/L). The third group had ALT >100 and was group 3.

The complete data regarding patient details along with history, platelet, ALT, PT, APTT, hepatomegaly, transfusions required, duration of hospital stay and PICU stay, repeat SGPT values, type of dengue and complications if any were collected in a pre formed proforma (Annexure). The formulated data was analysed statistically and co relation between the 3 groups with regard to symptomatology and lab parameters were assessed.

Statistical tools used

The data collected from the patients were first edited and tabulated. Microsoft Excel has been used to generate graphs, tables etc. Diagrammatic representations like bar diagram, pie diagrams are used to identify the contribution of different attributes in the thesis.

Descriptive data was analyzed using mean, median, range and percentage. The level of significance noted by

Significant (p value: $0.01<p\leq0.05$)

Strongly significant (pvalue: $p\leq0.01$)

Results on continous measurements are presented on mean +_SD (Min-Max) and results on categorical measurements are presented in number (%). Appropriate descriptive and inferential statistics were computed by means of SPSS software. Statistical independent t-test analysis was used for interpretation.

Results

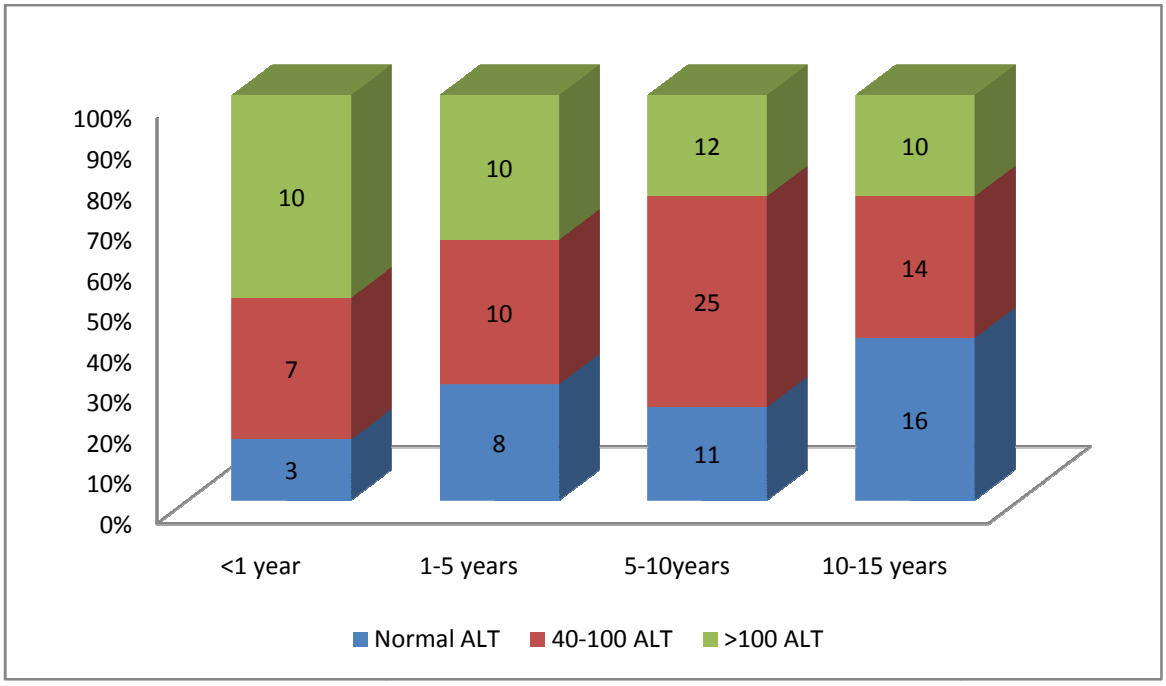
There were a total of 136 children with serology proven dengue infection during the study period. There were 87 boys and 49 girls included in the study.

Age Distribution: Table 1 shows the age distribution of the patients. There were 20 children less than 1 year of age, 28 children between 1 to 5 years of age, 37 children between 5 to 10 years of age and 40 children of age between 10 to 15 years. Out of these, 17 out of the 20 children (85%) below 1 year of age had elevated ALT, compared to 20 of 28 (71%) in the 1 -5 age group, 37 of 48 (77%) in the 5-10 age group and 24 of 40 (60%) in those over 10 years.

Table 1: ALT levels in different Age groups

Age distribution	Normal ALT	ALT 40-100	ALT >100	Total no & % with elevated ALT
< 1 yr	3	7	10	17/20 (85%)
1-5 yrs	8	10	10	20/28 (71.4%)
5-10 yrs	11	25	12	37/48 (77%)
10-15 yrs	16	14	10	24/40 (60%)

Figure 1: ALT levels in different Age groups

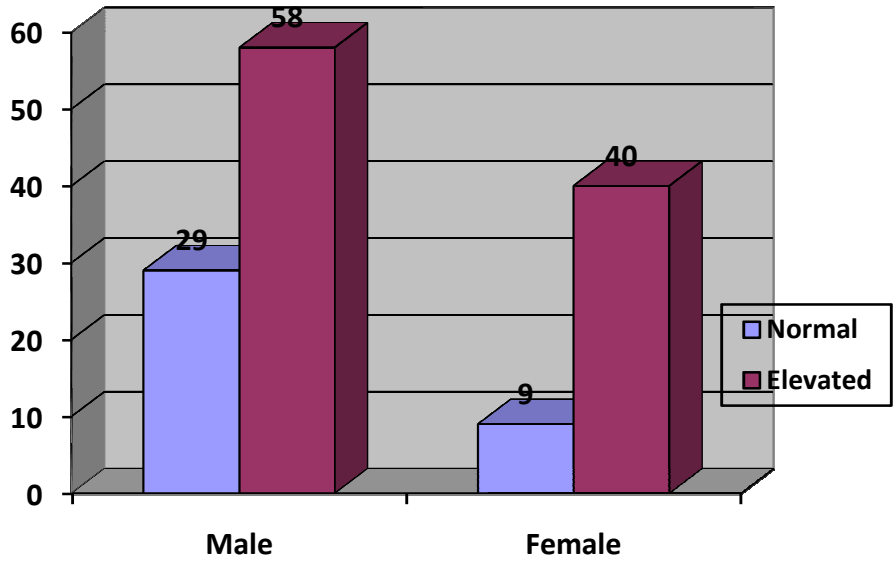


Sex Distribution: There were 87 males and 49 females. While 58 of the 87 males had elevated ALT (67%), 40 of the 49 females had elevated ALT (81.6%). (Table2)

Table 2: Association of ALT levels in both the sexes.

ALT level	Male	Female
Normal	**29/87 (33.3%)**	**9/49 (18.3%)**
Elevated	**58/87 (66.6%)**	**40/49 (81.6%)**
Total	**87**	**49**

Figure 2: Association of ALT levels in both the sexes.



Type of dengue: All cases (N=136) included in the study were serologically proven dengue cases. Out of this 36 children (26.4%) had primary dengue and 100 children (73.5%) had secondary dengue (table 3).

Table 3: Distribution of the type of Dengue infection

Type of Dengue	No :	Total
Primary infection	36	36/136 (26.4%)
Secondary infection	100	100/136 (73.5%)

Figure 1: Distribution of the type of Dengue infection.

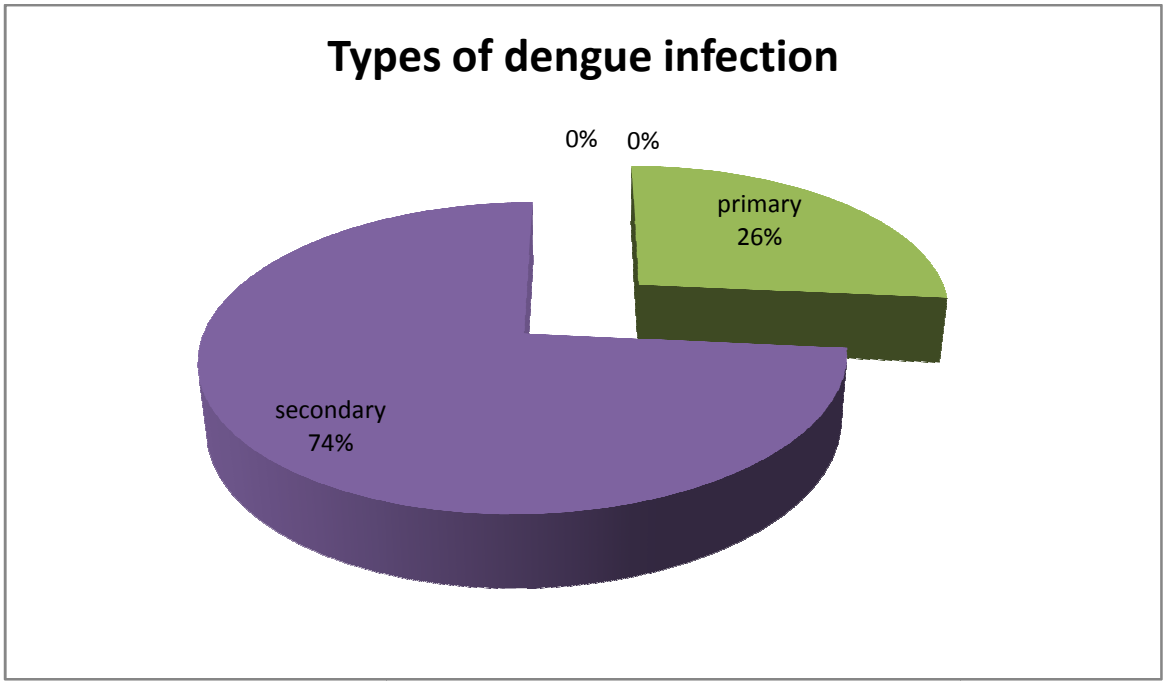


Table 4: Association of ALT values with Types of Infection

ALT value	Primary Dengue	Secondary Dengue
Normal	9 (23.6%)	29 (76.3%)
40 - 100	12 (21.4%)	44 (78%)
>100	18 (42.8%)	24(57.2%)

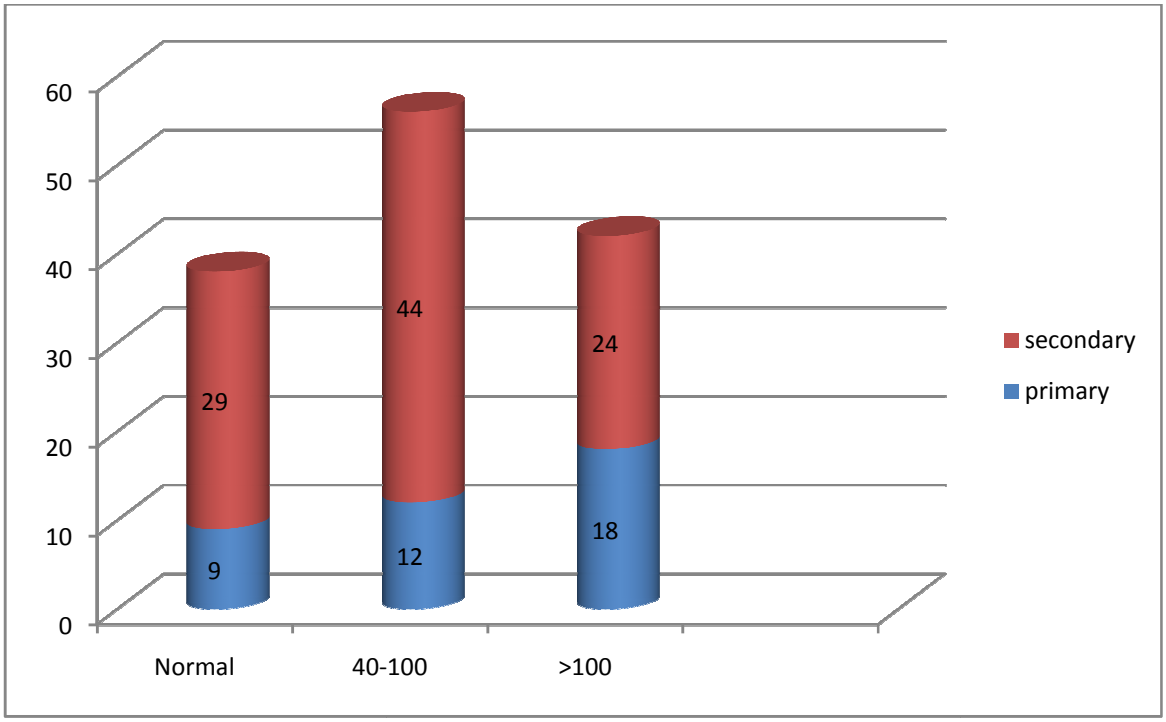


Figure 2: Association of ALT values with Types of Infection.

In the Table 4, the group with normal ALT values had 9 cases of primary dengue (23.6%) and 29 cases (76.3%) of secondary dengue. There were 12 cases (21.4%) of primary dengue and 44 cases (78%) of secondary dengue in the group with ALT levels between 40 to100. In the group with ALT levels >100 there were 18 (42.8%) primary dengue and 24 (57.2%) secondary dengue cases.

Among the 136 children, 98 had elevated ALT levels while in the remaining 38 children ALT value was normal (Table 5).

Table 5: Shows percentage of children with and without hepatitis.

ALT Level	Number	Percentage **%**
Normal ALT	38	27.9 %
Elevated ALT	98	72.1%
Total	136	100 %

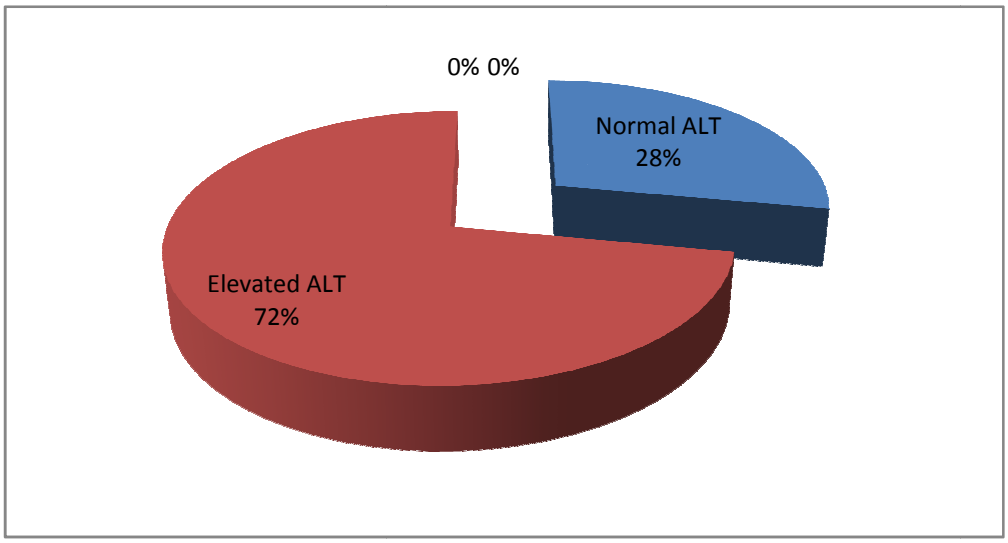


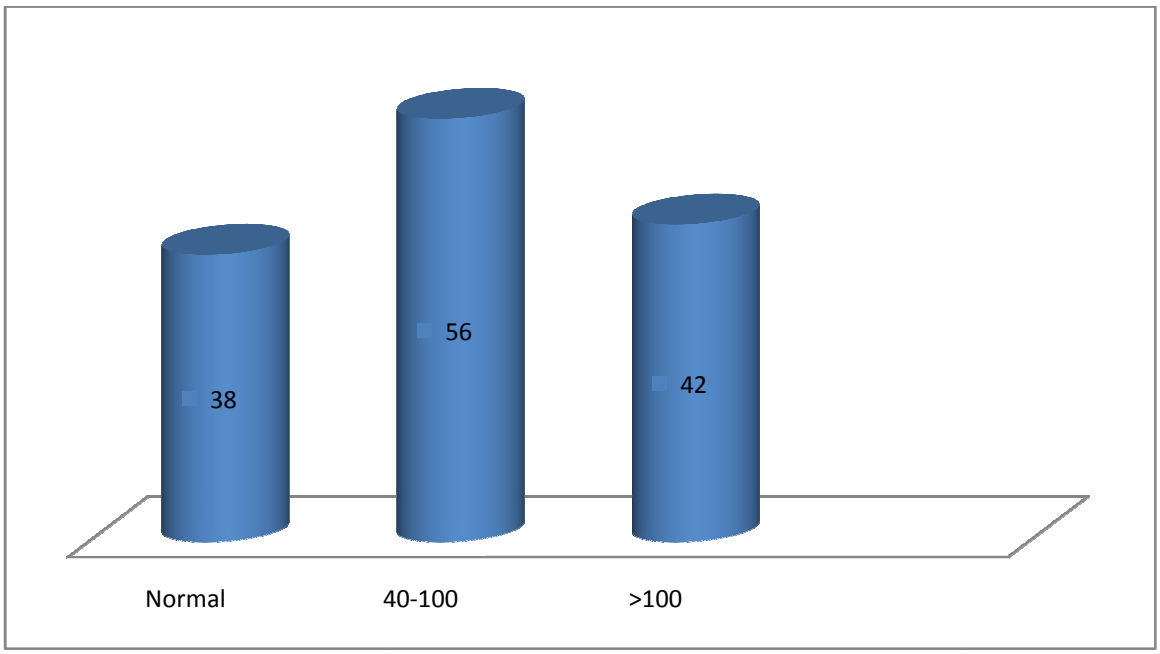
Figure 5: Shows percentage of children with and without hepatitis.

Among these 98 children, 56 had SGPT between 40 IU/L and 100 IU/L, while 42 had values above 100 IU/L (Table 6).

Table 6: **Distribution of ALT values in the study population**

ALT levels	No :	% within the study population
Normal	38	38/136 (28%)
ALT 40 - 100	56	56/136 (41%)
ALT > 100	42	42/136 (31%)

Figure 6: Distribution of ALT values in the study population



Hepatomegaly distribution: Palpable liver below the right coastal margin was seen in all children with elevated ALT levels. A few children with normal ALT levels did not have any liver palpable below the right coastal margin. The mean

value of palpable liver in the groups with normal ALT, ALT 40-100 and ALT <100 are 2.0526, 3.2500 and 3.7143 respectively. Children with ALT> 100 had the highest mean palpable liver and those with normal ALT had the lowest mean palpable liver. (table 7)

Table 7: Shows hepatomegaly in different ALT groups.

ALT values	No of children	Mean of palpable liver	F value	P value
Normal ALT	38	2.0526	19.379	P<0.01
ALT 40-100	56	3.2500		
ALT > 100	42	3.7143		
Total	136	3.0588		

In the above table F =19.379

For the mean difference in hepatomegaly between groups [ALT 40 -100, control group and ALT > 100] is significant. (P < .01)

Post Hoc tests

Table 8

Comparison of palpable liver size among the study group	**P value**
ALT Normal Vs ALT 40-100	<0.01
ALT Normal Vs ALT >100	<0.01
ALT 40- 100 Vs ALT > 100	0.184

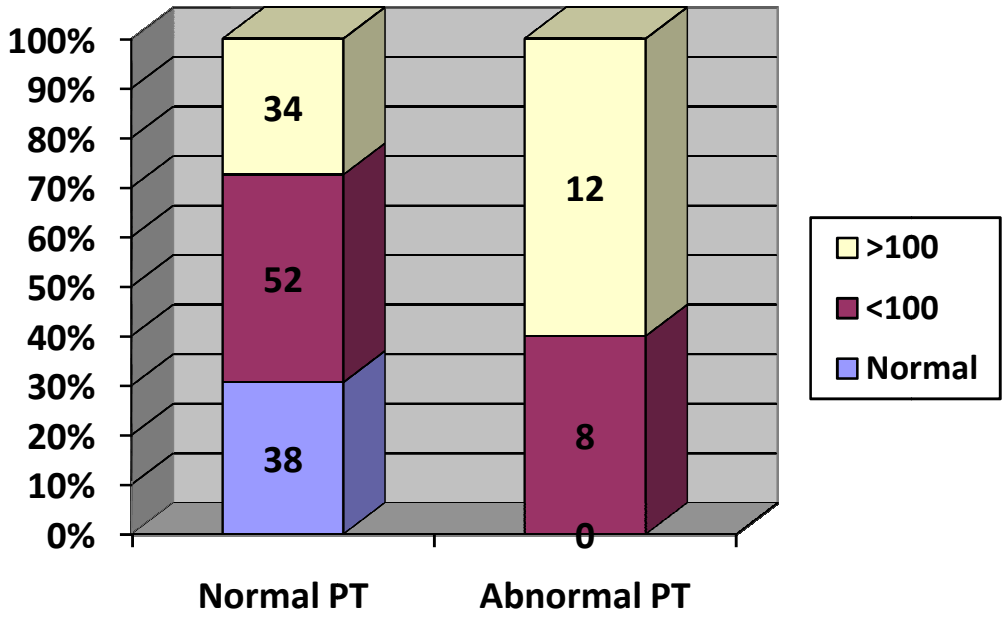
Further the post Hoc analysis (table 8) reveal that there is a significant association in palpable liver size between the groups with normal ALT and those with elevated ALT. Comparison of groups with normal ALT and ALT between 40 –100 is very significant ($p < 0.01$) which is similar to the significant association comparing the normal ALT group with ALT >100 ($p < 0.01$). However there is no significant association in hepatomegaly in the comparison between the study groups. P = .184

PT Profile: All the 38 children with normal ALT also had normal PT. However 8 out of 32 children (19%) with ALT > 100 IU/L had prolonged PT (p value 0.005). Only 4 of 56 children (7%) with ALT between 40 and 100 IU/L had prolonged PT. (table 9)

Table 9: ALT levels & its association with PT

ALT levels	Normal PT INR<1.1	Normal PT %	Abnormal PT INR>1.1	Abnormal PT %
Normal	38	38/38 (100%)	0	0%
<100	52	52/56 (92.8%)	4	4/56 (7.2%)
>100	34	34/42 (81%)	8	8/42 (19%)
Total	124	124/136 (91%)	12	12/136(8.8%)

Figure 3: ALT levels & its association with PT.

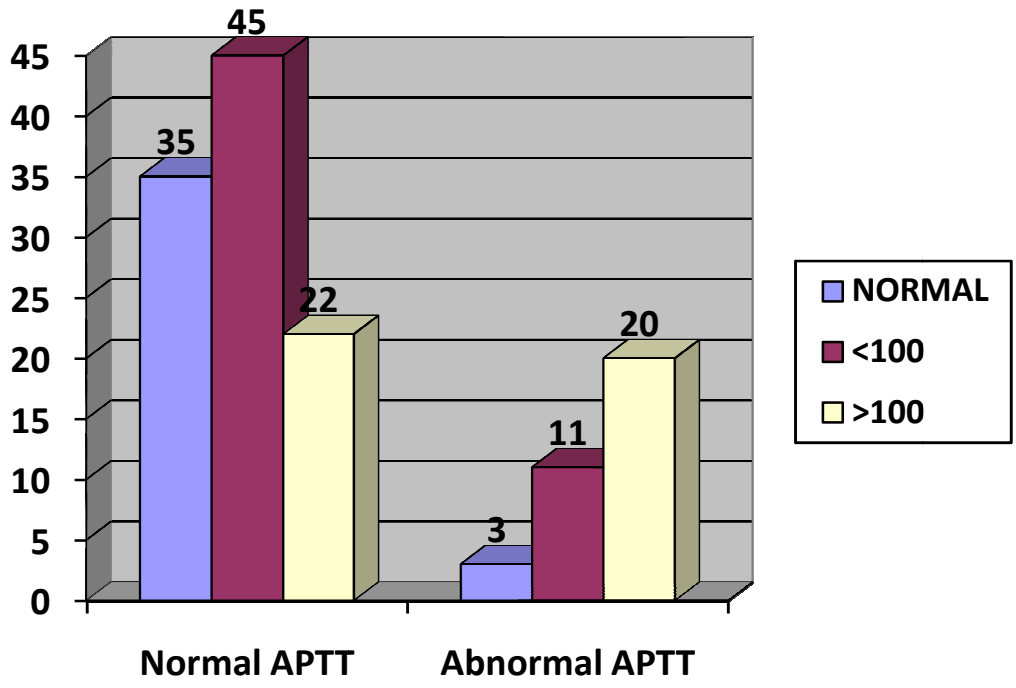


APTT Profile: Among the 38 children with normal ALT, only 3 (8%) had prolonged APTT, compared to 31 out of 98 children (31.6%) with elevated ALT (p value < 0.05). While only 11 out of 56 (19.6%) in the ALT 40 – 100 IU/L group had prolonged APTT, 20 out of 42(47%) in the > 100 ALT group had prolonged APTT (p value < 0.05).(table 10)

Table 10: ALT levels & its association with APTT

ALT levels	**Normal APTT**	**Normal APTT %**	**Abnormal APTT**	**Abnormal APTT %**
Normal	35	35/38 (92%)	3	3/38 (7.9%)
<100	45	45/56 (80%)	11	11/56 (20%)
>100	22	22/42 (53%)	20	20/42 (47%)
Total	102	102/136(75%)	34	34/136(25%)

Figure 4: ALT levels & its association with APTT.



Platelet drop distribution: Platelet drop was seen in all the three groups. The mean value of each individual group was calculated. The mean value of platelets in the normal group, ALT 40 – 100 and ALT > 40 were 70447.37, 46196.43 and 35000.00 respectively. The normal ALT group had the highest mean value whereas the group with ALT>100 had the lowest mean value. (Table 11)

Table 11: shows mean platelet value in different ALT groups.

ALT values	No of children	Mean platelet value	F Value	P value
Normal ALT	38	70447.37	15.037	<0.01
ALT 40-100	56	46196.43		
ALT > 100	42	35000.00		
Total	136	49514.71		

In the above table the F = 15.037. For the mean difference in platelet drop between groups [ALT < 100, control group and ALT > 100] is significant. (P<0.01)

Table 12: Post Hoc tests. Comparative significance of mean platelet count among the study group

Comparison	P value
ALT Normal Vs ALT 40-100	<0.01
ALT Normal Vs ALT >100	<0.01
ALT 40- 100 Vs ALT > 100	0.181

Further the post Hoc analysis (table 12) reveal that the there is a significant difference in the platelet drop when we compare the group with elevated ALT and the group with normal ALT levels. Comparison of groups with normal ALT and ALT between 40 –100 is very significant (p<0.01) which is similar to the significant association comparing the normal ALT group with ALT >100 (p<0.01). There is no significant association in platelet drop in the comparison within the groups with elevated ALT. (P = .181)

Table 13

Platelet value	ALT			Total
	Normal	ALT40-100	ALT>100	
< 10,000	0	3	6	9
10,000-20,000	4	5	9	18
Above 20,000	34	48	27	109
Total	56	56	42	136

In the above table 13 we can see the extent of platelet drop in each group. Platelet values below 10,000 were predominantly seen in the children with ALT >100. In the group with ALT > 100 six children had platelet below 10,000;9 children with platelet value between 10,000 – 20,000 and 27 children with platelets above 20,000. Out of 56 children in the group with ALT 40- 100; 3 children had platelet value below 10,000, 5 had between 10,000-20,000 and 48 children with more than 20,000. Majority of the children (34) in the normal ALT level had platelet value more than 20,000 whereas only 4 had platelet between 10,000 -20,000 and none of the children had it below 10,000.

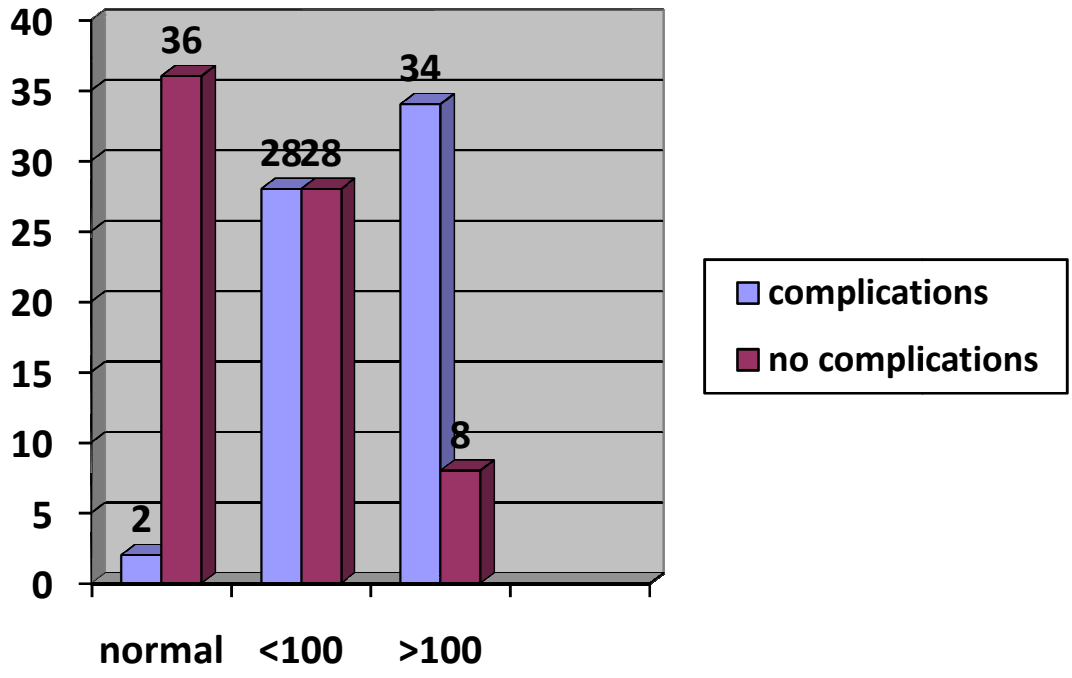
Complication: Only 2 children out of 38(5.3%) developed complications in comparison to 28 out of 56 (50%) children in group with ALT<100(P=.000) and 34 out of 42 (81%) children in the group with ALT>100(p=.000).The comparison within the groups ALT 40- 100 and ALT >100 is also significant

(p=.002).[table 14]. The common complications seen were hypotension, bleeding manifestations, shock and plasma leakage.

Table 14: ALT levels & its association with complications

ALT value	Complications (%)	No complications (%)
normal	2/38 (5.3%)	36/38 (94.6%)
< 100	28/56(50%)	28/56 (50%)
>100	34/42(81%)	8/42 (19%)
Total	64/136(47%)	72/136(53%)

Figure 5: **ALT levels & its association with complications.**

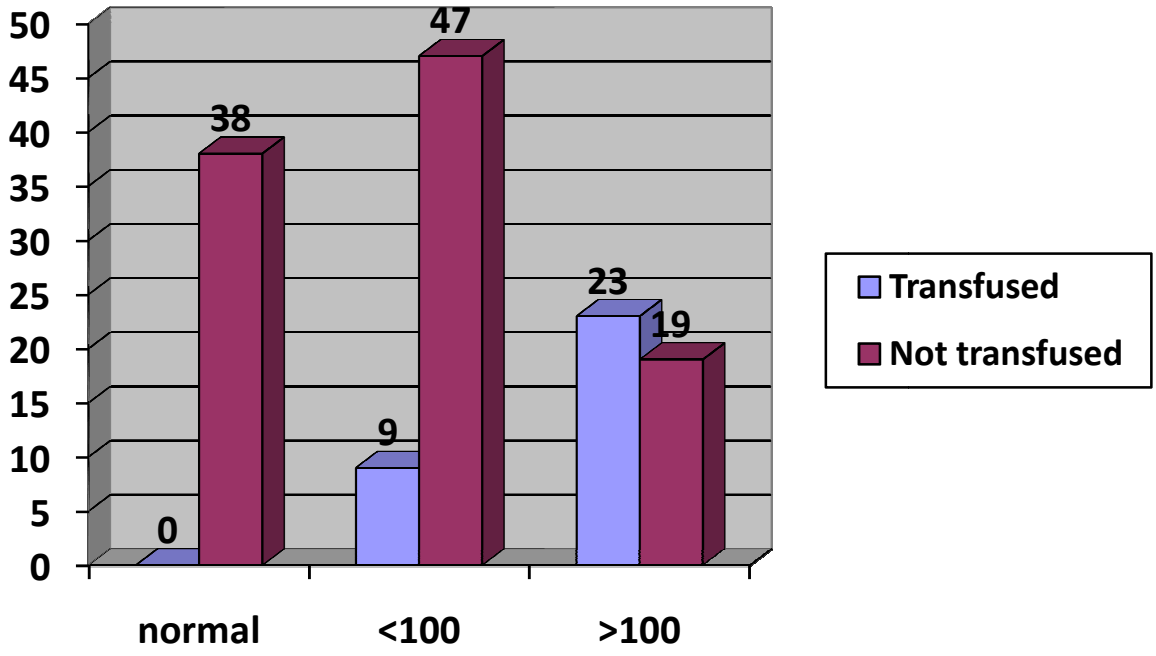


Platelet transfusions: In the group of 38 children with normal ALT levels none received any platelet transfusion while compared to the 32 out of 98 children (32.65%) with elevated ALT who received transfusion (p =.006). 23 out of 42 (55%) children in the group with ALT >100 received transfusions when compared to 9 out of 56(16%) children in the group with ALT between 40 and 100. (table 15)

Table 15: ALT levels association in Platelet transfusion

ALT levels	Transfused (%)	Not Transfused (%)
Normal	0(0%)	38 (100%)
<100	9/56 (16%)	47(84%)
>100	23/42 (55%)	19(45%)
Total	32/136 (23.5%)	104(76.5%)

Figure 10: ALT levels association in Platelet transfusion.



In majority of the cases platelet transfusions were given in cases of bleeding manifestations but for a few exceptions, where the transfusions were given prophylactically. Hence their significance of association was not calculated statistically.

FFP transfusion: The normal ALT group with 38 children received no FFP transfusion while compared to 9 out of 98 children in the group with elevated ALT levels(p=.053). 8 out of 42 children (19%) in the group with ALT> 100 received FFP transfusion while only one child out of 55(1.78%) in the group with ALT <100 received transfusion. (Table 16)

Table 16: ALT levels association in FFP transfusion.

ALT Values	Transfused (%)	Not Transfused
Normal	0%	38 (100%)
< 100	1/56 (1.8%)	55 (98.2%)
> 100	8/42 (19.04%)	34 (80.9%)
Total	9/136 (6.6%)	127 (93.4%)

Again the indications for FFP transfusions was not standardised and their association of significance was no calculated statistically.

Hospital stay duration distribution: The duration of hospital stay varied from group to group. The maximum period of hospital stay seen was 15 days and the minimum was 3 days. The mean of hospital stay duration was calculated and it was found that the mean of groups with normal ALT, ALT 40-100 and ALT>100 were 4.8421, 5.1250 and 6.2619 respectively. The mean of hospital stay was seen to be higher in children with ALT>100 when compared to the other two groups. (Table 17)

Table 17

ALT values	No of children	Mean of Hospital stay	F VALUE	P VALUE
Normal ALT	38	4.8421	9.84	<0.01
ALT 40-100	56	5.1250		
ALT > 100	42	6.2619		
Total	136	5.3971		

In the above table F = 9.843

For the mean difference in duration of hospital stay between groups [ALT < 100, control group and ALT > 100] is significant. (P <0.01)

Table 18: Post Hoc tests. Comparative association in hospital stay duration among the groups.

Comparative groups	P value
ALT Normal Vs ALT 40-100	0.686
ALT Normal Vs ALT >100	<0.01
ALT 40- 100 Vs ALT > 100	<.01

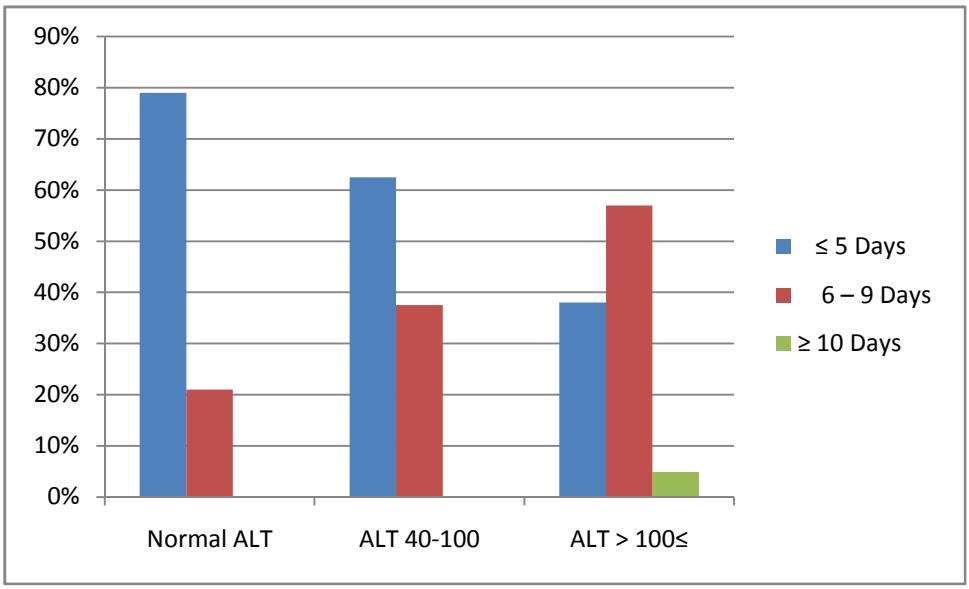
Further the post Hoc analysis (table 19) reveal that there is a significant difference in the duration of hospital stay in children with SGPT > 100 when compared to the other two groups. . Comparison of groups with ALT>100 and ALT between 40 –100 is very significant (p=.002) which is similar to the significant association comparing the normal ALT group with ALT >100(p=.000).However There seems to be no significant association between the groups with normal ALT level and the group with ALT 40-100. (p=.686)

Table 20: shows distribution of hospital stay in correlation with ALT value

	HOSPITAL STAY		
ALT Level	**≤ 5 Days**	**6 – 9 Days**	**≥ 10 Days**
Normal ALT	30/38 (79%)	8/38 (21%)	-
ALT 40-100	35/56 (62.5%)	21/56 (37.5%)	-
ALT > 100	16/42 (38%)	24/42 (57%)	2/42 (4.8%)

Table 20 above shows the distribution of duration of hospital stay of all the 136 children. Out of the 38 children with normal ALT levels, 30 children (79%) stayed in hospital ≤5 days and only 8 children (21%) stayed more than 5 days. where as in the group with ALT 40 -100 with 56 children, 35 (62.5%)stayed in hospital ≤5 and 21 children (37.5%) stayed longer than 5 days. In the group with ALT>100 with 42 children, 16(38%) of them stayed ≤5 days and 24 children (57%) stayed more than 5 days. This is the only group where 2 (4.8%) children stayed longer than 10 days.

Figure 11: shows distribution of hospital stay in correlation with ALT value



Duration of PICU stay: Children who were admitted sick or developed complications in the ward were kept in PICU. The mean PICU stay was calculated for all the 3 groups. The mean of duration in PICU stay of children

with control group, SGPT < 100 and SGPT > 100 were 0 .1053, 1.4286 and 3.0476 respectively. Children with ALT levels more than 100 were seen to have the highest mean for PICU stay duration. (table 21)

Table 21: Mean hospital stay in children in relation with ALT levels.

ALT values	No of children	Mean of PICU stay	F value	P value
Normal ALT	38	.1053		
ALT 40-100	56	1.4286		
ALT > 100	42	3.0476	33.390	P<0.01
Total	136	1.5588		

In the above table F = 33.390

For the mean difference in duration of stay in PICU between groups [ALT < 100, control group and ALT > 100] is significant. (P < 0.01)

Table 22: Post Hoc tests. Comparative association in PICU stay duration among the groups.

Comparative groups	P value
ALT Normal Vs ALT 40-100	< 0.01
ALT Normal Vs ALT >100	<0.01
ALT 40- 100 Vs ALT > 100	<0.01

Further the post Hoc analysis (table 22) reveals that there is a significant association in PICU stay duration between all the 3 groups.

Table 23: Distribution of PICU stay duration in relation to ALT levels.

PICU stay	NIL	≤ 5 Days	6 - 9 days	≥ 10 days
Normal ALT	36/38 (95%)	2/38 (5%)	-	-
ALT 40-100	27/56 (48.2%)	26/56 (46.4%)	3/56 (5.3%)	-
ALT > 100	7/42 (16.6%)	31/42 (73.8%)	3/42 (7.1%)	1/42 (2.4%)

Figure 12: Distribution of PICU stay duration in relation to ALT levels.

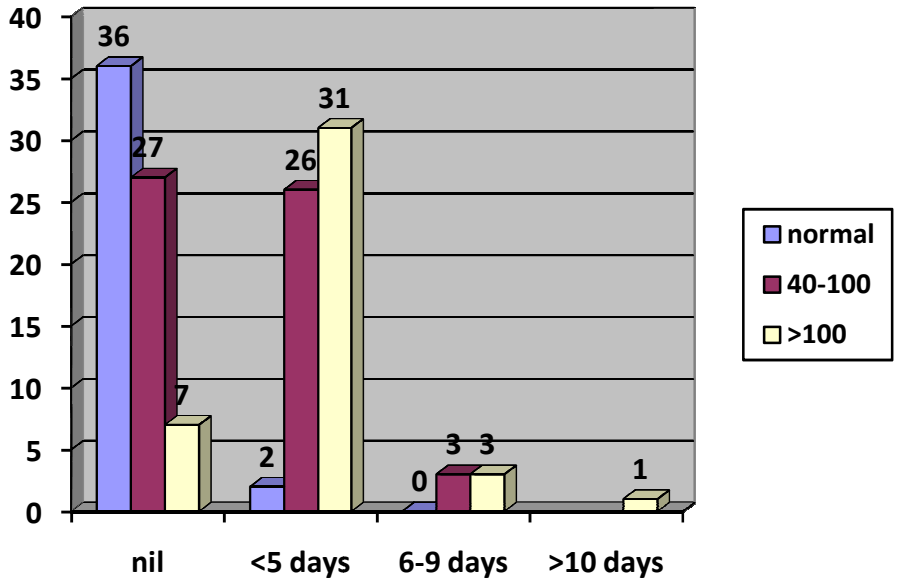


Table 23 above shows the distribution of children who stayed in the PICU. In the total study group of 136 children only 66 children (48.5%) stayed in PICU. In 38 children with normal ALT only 2 children had to stay in PICU and that too for ≤ 5 days. Out of 56 children with ALT 40-100 level 29 (51.7%) children stayed in the PICU in which 26 children (46.4%) stayed ≤ 5 days and 3

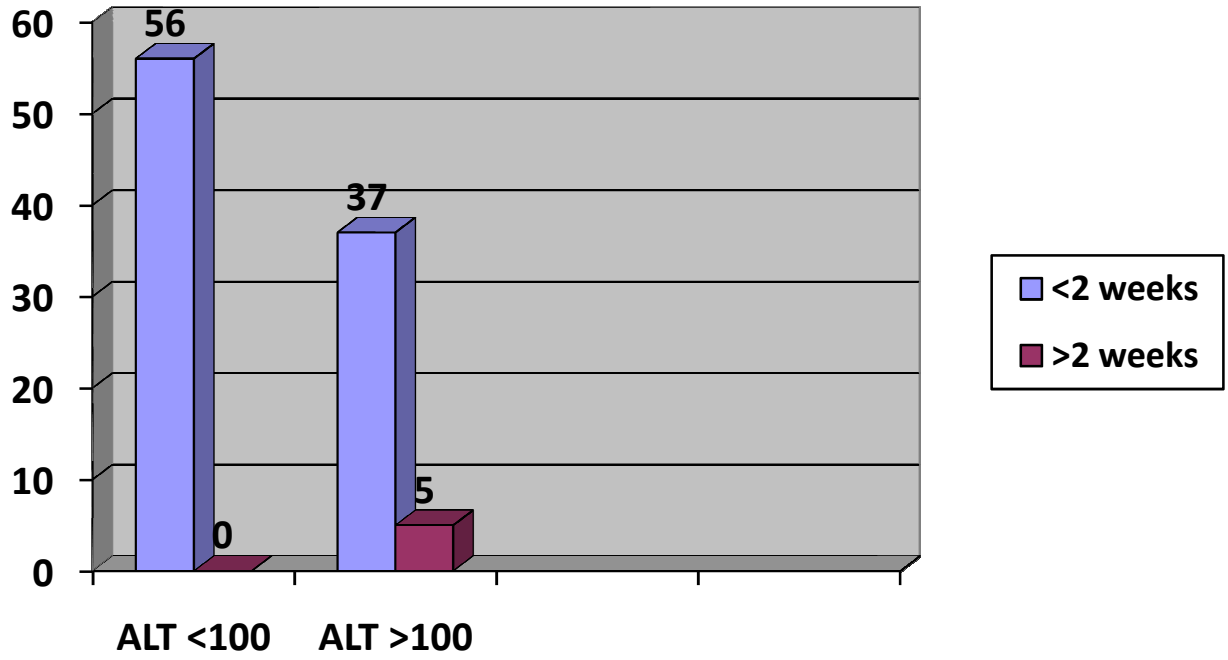
children (5.3%) stayed for more than 5 days. It is only in the group with ALT>100 where one child stayed longer than 10 days. Out of 42 children in this group 31 children (73.8%) stayed less ≤ 5 days and 3 (7.1%) of them stayed more than 5 days.

Repeat ALT values: time taken to recover- Majority of the children with elevated ALT values returned to normal within 2 weeks. In the group with ALT 40 – 100,the ALT values returned to normal in all the 56 children where as 5 out of 42 (5%) children in the group with ALT>100 took more than 2 weeks and the remaining 37 children in less than 2 weeks. (Table 24) 95% of the elevated ALT values returned to normal in 2 weeks.

Table 24: Time duration for normalisation of ALT values

Time taken for ALT to normalise	**ALT <100**	**ALT>100**	**Total**
Less than 2 weeks	56	37	93/98 (95%)
More than 2 weeks	0	5	5/98 (5%)
	56	42	98

Figure 13: Time duration for normalisation of ALT values



DISCUSSION

Dengue is prevalent worldwide and numerous studies are done across the globe. Majority of the literature is available from the developing countries of South East Asia. In this study we aim to study the incidence and degree of hepatic dysfunction in children less than 15 yrs admitted with serologically proven dengue infection.

Type of dengue: Out of the total 136 children with serologically proven dengue, 100 cases were found to be secondary dengue (73.5%) and remaining 36 were primary (26.5%). In the study done at Apollo hospital, Chennai, Fifty-one children (46.7%) had primary dengue infection and 45 (41.2%) had secondary dengue infection (48). Of the children with elevated ALT, 27 children had primary dengue infection (27.6%) and 71 children had secondary dengue (72.4%) whereas in the group with normal ALT, 9 were primary dengue infection (23.7%) and 29 children had secondary dengue infection (76.3%). From our data, we have seen a predominance of secondary dengue over primary dengue though it is statistically not significant. The reason for the predominance in secondary dengue infection is that many of the children live in dengue endemic areas and there is a high chance that they have been exposed to dengue earlier.

Percentage of hepatitis: In our study with 136 consecutive serologically proven dengue cases, 98(72.1%) children developed hepatitis as evidenced by elevated ALT levels. Mohan et al in 2000 found 96% of children in his study to have elevated transaminase level (49).

Age distribution: All age groups were equally affected. However hepatic involvement was more predominant in children aged less than one year. Suchithra Ranjith et al, in her study states that severe disease occurred most often in infants followed by the 1–5 year age group (48).

Out of the 20 children aged less than 1yr included in the study, 17 had elevated SGPT levels (85%). Children aged more than 10 were seen to be affected slightly lesser when compared to the other age groups. Statistically the association between age and elevation of SGPT was found to be insignificant. (p= .160)

Sex distribution: In the consecutive 136 children, 87(64%) were boys and 49 were girls (36%). The group with elevated ALT had 59.19% boys and 40.81% girls whereas the normal ALT group had 76.31% boys and 33.69% girls. There was no statistically significant finding either in the incidence of dengue or elevation of ALT based on the sex of the child. Similar results were seen in the study from Chennai done in Apollo hospitals where there was no sex predilection (48).

Coagulation profiles: Both PT and APTT were evaluated for all the patients.

PT**:** Only 12 children had abnormal PT values. None of the children in the normal ALT group had abnormal PT values. We found 18% of the total study population with prolonged PT. In a study from Mysore, Kalenahalli Jagadishkumar et al found prolonged PT in 20% of children with Dengue infection which is similar to our result (50). Study done by Suchitra Ranjith in 2006 shows disordered coagulation (prolongation of the prothrombin and/or partial thromboplastin time) was seen in 74 children (67.8%)(48). Out of the 12 children with abnormal PT values, 8 children had ALT >100 whereas the other group with ALT < 100 had 4 children. Our study shows that children with elevated ALT levels are at a higher risk of developing prolonged prothrombin time and thereby bleeding when compared to children with normal ALT levels. However there is no significant association seen within the groups with elevated ALT levels.

APTT: In the group with elevated ALT levels 31 children (31.63%) had abnormal APTT levels. 64.51% of the children with abnormal APTT levels belonged to the group with ALT>100. In the normal ALT group only 3 children had prolonged APTT. From the study it is seen that prolonged APTT is predominantly seen in children with elevated ALT levels when compared to the children with normal ALT value. It was also found that ALT values correlated with the elevation of APTT. There was a rise in APTT value as there is a rise in ALT level.

Platelet drop: Out of 9 children with platelet value < 10,000, 66.6% had ALT>100. In those children with platelet value between 10,000 and 20,000, 62.48% had ALT >100. In the 136 children 19.8% had platelet value below 20,000 which is quite similar to the study done by Gurudeep S.Dhooria (51). Platelet counts less than 50,000/cumm was noted in 62.3% in the study done by Suchitra Ranjith (48). In the control group 89.47% had platelet value >20,000. There is a statistically significant association between drop in platelet count while comparing normal ALT group and the group with ALT<100 ($p<0.01$). Similarly the association is significant comparing normal ALT group with the ALT >100 group ($p<0.01$). Within the ALT elevated groups there has been no significant association in platelet drop ($p=0.181$). The study shows that children with elevated ALT levels are at a higher risk of developing thrombocytopenia when compared to those with normal ALT value. However the degree of ALT elevation has got no correlation with the fall of platelets.

Hepatomegaly: Hepatomegaly was clinically observed in all the children in the study group. In the total of 136 children, 91% had hepatomegaly which is similar to the study done by Kalenahalli Jagadishkumar et al in Mysore which showed hepatomegaly of 96% (50). Petddachai and Faridi et al reported hepatomegaly in all children with severe dengue (4, 16). In the elevated ALT group, 15 children had hepatomegaly (4cm liver palpable below the right coastal margin) against only one child in the normal ALT group. In the normal

ALT group 28.94% of children did not have hepatomegaly. Statistical analysis has shown that the mean difference in hepatomegaly between the normal and elevated ALT group is significant ($p<0.01$). There seems to be no statistical significance in mean difference in hepatomegaly within the groups with elevated ALT ($p=.184$). The study shows that there is an increase in the liver size as the ALT value is elevated but the level of ALT elevation has no significant correlation with the palpable liver size.

Complications: Complications were seen in all the 3 groups. Complications were very minimal in the control group. The common complications seen were hypotension, bleeding manifestation, shock and plasma leakage. Only 2 out of 38 children (5.26%) in the control group developed complications where as 62/98 children in the study group (63.26%) developed complications. There seems to be a significant association in complications comparing control group with the study group ($p<0.01$) and also within the study groups ($p<0.01$). The study shows that complications occur more frequently when the level of ALT is very high. There was an increasing trend to develop complications as and when the ALT values were rising.

Platelet transfusion: In majority of cases**,** platelets were transfused when children developed bleeding manifestations. In few children, prophylactic transfusion was carried out as decided by the treating unit. A total of 32 children received transfusions. Only 2 out of the 32 children had normal ALT. In the

study group with ALT>100 there were 8 children who received more than 2 transfusions. Statistical correlation was not done because on few instances prophylactic transfusions were also given. However it could be concluded from the study that the necessity of transfusion is on the higher side for children with elevated ALT levels.

FFP transfusions: None of the children in the control group received transfusions. In the elevated ALT group 9 children received FFP transfusions. Out of the 9 children 88.88 % had ALT> 100. No statistical analysis was done because the indication for FFP transfusion was not standardised. Then again the study shows that majority of the transfusion was given for children with very high ALT value.

Duration of hospital stay: The minimal duration of hospital stay was 3 days and the maximum duration was 15 days. In the elevated ALT group 51 out of 98 (52.04%) children stayed up to 5 days and 45/98 (45.91%) stayed more than 5 days. Only 2 children in the study group stayed longer than 10 days. In the control group 30/38 children (78.94%) stayed up to 5 days and only 8/38 children (21.05%) stayed longer than 5 days. None stayed more than 10 days. There is a significant association in the mean duration of hospital stay between the study group ALT>100 and the other two groups ($p<0.01$). We infer from the study that children with normal ALT values and those with mild elevation in ALT do not have much difference in their duration of hospital stay. However

Children with higher ALT values tend to stay for longer period of time in the hospital when compared to those with normal and mild elevation of ALT.

PICU stay: A total of 66 children stayed in PICU from all the 3 groups. From the normal ALT group there were only 2 of them (5.26%) and both of them stayed less than 5 days. Among the elevated ALT group 64/98 (65.30%) stayed in PICU. In this 64; 57 children stayed up to 5 days (89.06%) and only 6 of them stayed longer than 5 days. Only one child in the whole study stayed longer than10 days in PICU. Statistical analysis reveal that there is a significant association in the duration of stay in PICU between all the 3 groups ($p<0.01$). Study shows that children with very high values tend to stay longer in the PICU than the other 2 groups. Children with mild elevation of ALT values also stay longer than those with normal ALT value.

Time taken for normalisation of ALT: Majority of the children with elevated ALT values returned to normal within 2 weeks. In the group with ALT 40 – 100, the ALT values returned to normal in all the 56 children where as 5 out of 42 (5%) children in the group with ALT>100 took more than 2 weeks and the remaining 37 children in less than 2 weeks. All the 5 children's ALT values had normalised when the test was repeated at one month. In all 98 children with raised liver enzymes, Hepatitis A, Hepatitis B and Hepatitis E were excluded by appropriate investigations. None of the children developed clinical jaundice and none developed fulminant hepatic failure.

CONCLUSION

1. 72.1% of children in the study population developed hepatitis.
2. Prolonged APTT is predominantly seen in children with elevated ALT levels.
3. Children with elevated ALT levels are at a higher risk of developing prolonged prothrombin time.
4. Children with elevated ALT levels are at a higher risk of developing thrombocytopenia; however the degree of ALT elevation has got no correlation with the fall of platelets.
5. There was an increasing trend to develop complications as and when the ALT values were rising.
6. The study shows that majority of the transfusion was given for children with high ALT value.
7. Children with normal ALT values and those with mild elevation in ALT do not have much difference in their duration of hospital stay however children with ALT values more than 100 tend to stay for longer period of time in the hospital.
8. Children with very high values tend to stay longer in the PICU.

9. Every child with hepatitis because of Dengue infection normalised their ALT value in less than one month.
10. None of the children developed clinical jaundice and none developed fulminant hepatic failure.

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ABBREVATIONS

DF	- DENGUE FEVER
DHF	- DENGUE HEMORRHAGIC FEVER
DSS	- DENGUE SHOCK SYNDROME
AE	- AEDES
WHO	- WORLD HEALTH ORGANISATION
DEN 1, 2, 3 & 4	- DENGUE VIRUS SEROTYPES 1, 2, 3 AND 4
IgG, IgM	- IMMUNOGLOBULIN G AND M
ELISA	- ENZYME LINKED IMMUNOSORBENT ASSAY
PCR	- POLYMERASE CHAIN REACTION
Hb	- HEMOGLOBIN
PCV	- PACKED CELL VOLUME
SGPT	-SERUM GLUTAMATE OXALO-ACETATE TRANSAMINASE

SGOT	-SERUM GLUTAMATE PYRUVATE TRANSAMINASE
FFP	- FRESH FROZEN PLASMA
ALT	- ALANINE AMINO TRANSFERASES
PICU	- PAEDIATRIC INTENSIVE CARE UNIT

PROFORMA

NAME : AGE: SEX: UNIT:

OP NO: DOA: DOD: WEIGHT:

CLINICAL FEATURES	YES	NO
IRRITABILITY		
ERYTHEMA		
PETICHIAE		
MALENA		
OTHER BLEEDING MANIFESTATIONS		
COLD EXTREMITIES		
PUFFINESS OF FACE		
ASCITES		
HEPATOMEGALY		
PLEURAL EFFUSION		
JAUNDIC		
ENCEPHALOPATHY		

LABORATORY DATA

DAY OF STAY:				
TOTAL COUNT				
DC				
PCV				
HB				
PLATELT COUNT				
ESR				
PERIPHERAL SMEAR				
PT				
APTT				
SGPT				
XRAY CHEST				

DENGUE SEROLOGY	**POSITIVE**	**NEGATIVE**
IgM		
IgG		

S.NO	NAME	IP NO	A	S	SG	PL	PT	AP	LS	T	RS	D	C	D H	PS
1.	SHIFANA	I11017867	5Y	F	62	38000	13.6	38	3	2 P	19	2	+	4	2
2.	SIVA SANKARI	I11018062	10Y	F	68	48000	12.8	41.8	2	-	27	2	-	6	-
3.	HARI.P	I11018067	10Y	M	219	9000	14.9	46.1	8	2 F	38	2	+	5	3
4.	ANTO.M	I11018075	7Y	M	490	14000	13.5	43.5	5	2 P	54	2	+	5	3
5.	BRINDHA	I11019022	9Y	F	129	8000	15	39.3	5	2 P	34	2	+	8	3
6.	GOWTHAM	I11019348	8Y	M	64	18000	19.2	47.2	5	4 P	24	2	+	7	5
7.	BHARTHINI	I11019706	6Y	F	48	5000	13.8	40.1	4	2 P	18	2	+	7	5
8.	DAVID	I11019961	9Y	M	95	91000	12.7	32.3	3	-	32	2	-	5	-
9.	SITHARTHAN	I11020135	10Y	M	94	35000	11.8	33.4	3	-	28	2	+	4	-
10	BOOVESH	I11020317	7 M	M	49	97000	12.6	31.4	3	-	24	1	-	6	-
11	VENKADESH	I11020328	4Y	M	122	35000	13.8	52.7	3	-	32	2	+	9	4
12	SAHANA	I11021486	8M	F	1348	22000	31.9	76.7	4	4P&2F	81	1	+	15	11
13	VARSHA.SRE	I11022635	3Y	F	350	4000	37.4	91.1	4	2 P	36	2	+	5	3
14	MOUNISH	I11022919	8M	M	594	24000	16.3	67.3	5	4P&IF	38	2	+	10	9
15	MADHU.P	I11023643	9Y	M	55	7000	13.5	32.4	7	2 P	18	2	+	5	3
16	VISHWANTH	I11024589	14Y	M	62	30000	14.5	37.6	3	-	28	2	+	4	2
17	AISWARYA.R	I11024989	4Y	F	67	26000	12.8	42.6	3	-	31	2	+	5	4
18	NAGA GAYATHRI	I11025185	12Y	F	59	60000	13.3	33.5	3	-	24	1	+	5	4
19	SACHIN	I11025509	9M	M	156	60000	13.2	37.3	3	-	34	1	_	5	-
20	AISWARYA.S	I11025669	11Y	F	168	21000	14.9	48.2	3	-	29	2	+	5	2

S.NO	NAME	IP NO	A	S	SG	PL	PT	AP	H	T	RS	T	C	D I H	P S
21	UTESH	I11027020	7Y	M	230	15000	16.2	39.2	4	1 P	31	2	+	8	3
22	DEVADARSHINI		13Y	F	81	31000	13.6	36.7	3	-	30	2	-	4	-
23	SOWMIA	I11027777	12Y	F	45	72000	12.4	30.6	3	-	28	2	-	6	-
24	TAMILARASI	I11028120	9Y	F	260	24000	13.4	44.8	4	-	30	2	+	5	4
25	NAGA DEVI	I11028178	11Y	F	65	59000	13.1	31.2	4	2 P	27	2	+	4	2
26	DHAKSHAN	I11028304	2Y	M	339	50000	14.5	56	3	-	38	1	-	8	3
27	ASHWIN	I11028862	14Y	M	65	76000	12.8	30.6	2	-	23	2	-	4	-
28	DEEPAHARI	I11028862	4Y	M	88	30000	12.4	39.2	3	-	31	1	+	6	4
29	AKSHATHA	I11029359	7M	F	325	18000	12.7	39.2	3	2 P	34	1	+	9	4
30	SANDEEP	I11029826	10M	M	144	30000	12.4	38.3	4	-	28	1	+	6	4
31	SHRI MANGAI	I11031653	8Y	F	66	79000	12.5	41.2	3	-	29	2	+	5	3
32	THARUN	I11033038	10M	M	623	60000	13.3	52.1	6	1P&2F	34	1	+	9	7
33	KEERTHANA	I11033216	6Y	F	142	93000	13	30.8	5	-	32	1	-	6	-
34	NAVIYA	I11033804	3Y	F	309	36000	12.5	30.3	3	2 P	33	2	+	5	2
35	SUBHASREE	I11034230	2Y	F	270	14000	13	45.4	3	4 P	44	2	+	6	4
36	SURUTHIKA	I11034454	7Y	F	148	17000	13.7	43.5	3	2 P	38	2	+	7	4
37	NAVNEETHAN	I11035056	8Y	M	89	19000	12.8	37	3	-	32	2	+	6	3
38	BHOOMIKA	I11035175	5Y	F	75	28000	12	28.9	3	-	32	1	+	3	2
39	NITESH	I11035192	1Y	M	104	98000	12.8	30.4	4	-	22	1	-	6	-
40	JEEVANANTHM	I11035296	13Y	M	130	16000	13.1	38.7	3	3P&1F	34	2	+	6	3

S.NO	NAME		A	S	SG	PL	PT	AP	LS	T	RS	T	C	D	PS
41	SHAMEESHA	I11035449	5M	F	68	37000	19	45.9	3	2P&1F	22	1	+	9	4
42	LOKESH	I11035635	7Y	M	54	86000	13.2	30.2	5	-	29	2	-	4	-
43	SANKARA.N	I11036184	12Y	M	122	7000	12.5	37.4	6	3 P	37	2	+	6	4
44	MUGESH	I11036304	2Y	M	51	23000	11.9	37.6	3	-	27	2	+	5	1
45	KARTHIKEYAN	I12000806	10Y	M	134	10000	14.1	40.1	3	5 P	37	2	+	7	4
46	SHYAM	I12000849	6Y	M	85	36000	13	33.1	2	-	27	2	+	5	2
47	SIMIKA	I12001275	7Y	F	56	55000	11.9	34.6	2	-	31	2	-	4	-
48	SARATH	I12001363	11Y	M	124	9000	13.6	34.3	4	2 P	32	2	+	6	3
49	YOGESHWAR	I12001368	8Y	M	47	40000	13.2	31.2	3	-	28	2	+	6	2
50	ABISH	I12001841	4Y	M	68	21000	13.6	34.2	4	-	28	2	+	6	3
51	SUDHAN	I12001864	12Y	M	131	88000	12.4	29.4	3	-	45	2	+	5	3
52	DEVI PRASATH	I12001939	11 M	M	85	28000	12	46.3	5	-	35	2	+	9	5
53	DHARSHINI.P	I12002187	4Y	F	76	16000	13.2	31.6	3	-	32	2	+	6	3
54	ASHWITHA	I12002408	14Y	F	219	22000	15.3	35.2	3	1 P	34	2	+	7	3
55	PAVITHRA	I12002977	8Y	F	44	10000	12.6	39.6	5	2 P	28	2	+	5	2
56	SANTHANA	I12014321	11Y	M	325	38000	13.4	44.4	4	-	34	2	+	7	3
57	KISHORE	I12014983	8Y	M	80	44000	12.3	33.7	2	-	31	2	+	6	2
58	AMIR	I12009346	5Y	M	42	25000	14	36.5	4	-	30	2	-	6	-
59	VARSHASHRI	I12009568	6Y	F	59	45000	12	27.9	3	-	22	2	-	6	-

S.NO	NAME		A	S	SG	PL	PT	AP	LS	T	RS	T	C	D	PS
60	DIVAHAR	I12009805	7Y	M	64	60000	12.9	30.1	3	-	28	2	-	4	-
61	DHARNISH	I12011582	4M	M	258	28000	12.8	40	3	3P&2F	36	1	+	7	5
62	LOGESH	I12013550	10Y	M	53	62000	12.7	30.7	4	-	27	2	-	6	-
63	VISHANTH	I12013759	5Y	M	52	96000	12.3	31	5	-	26	2	-	4	-
64	DEEPAK .S	I12015134	14Y	M	48	81000	12.7	30.3	2	-	22	2	-	5	-
65	SHAHANA	I12015493	4M	F	851	32000	26.7	66.5	4	3P&2F	56	1	+	5	-
66	SABARIWASAN	I12015747	12Y	M	56	94000	12.8	30.3	2	-	28	2	-	5	-
67	KOKILA B%	I12015912	8M	M	52	51000	15.5	51.0	4	-	31	1	+	6	-
68	PRAKASH	I12016826	4Y	M	81	40000	12.9	41.4	3	-	37	2	+	6	2
69	ARISUDHAN	I12018753	11Y	M	85	45000	12.8	31.4	3	-	31	2	-	6	-
70	SREE VANSHIKA	I12018939	11M	F	339	22000	13.8	38.5	4	1 P	35	1	+	6	4
71	BHUVANSWARI	I12019211	13Y	F	95	29000	13.3	34.5	3	4 P	33	2	+	5	3
72	MEGAVARSHNI	I12019626	3Y	F	128	15000	13.4	36.3	4	-	34	1	+	6	3
73	LOHIT	I12019944	9Y	M	152	53000	12.9	29.5	2	-	28	2	+	4	-
74	SAI PRAVEEN	I12024546	9M	M	105	30000	13.5	44.9	3	-	36	1	-	6	2
75	KIRUTHIKA	I12019952	8Y	F	48	52000	13.4	37.2	3	-	26	2	-	5	-
76	GAYATHRI	I12020263	11Y	F	61	16000	13.1	34.5	3	-	33	2	-	5	-
77	AMBRITHA	I12020383	12Y	F	51	30000	12.9	43.1	2	-	22	2	+	5	1
78	KAMALESH	I2025688	11M	M	87	54000	13.8	36.5	4	-	30	1	-	6	2
79	PRIYANKA	I12021146	11Y	F	87	59000	13.1	33.4	4	-	31	2	-	3	-

S.NO	NAME		A	S	SG	PL	PT	AP	LS	T	RS	T	C	D	PS
80	SUDHARSHAN	I12021998	2Y	M	221	42000	14.2	36.4	3	-	38	2	-	4	2
81	YOGARAJ	I12022479	9Y	M	43	98000	12.8	31.4	2	-	17	1	-	4	-
82	SANGMITHRA.C	I12026689	11M	F	93	37000	11	29.0	2	-	24	1	-	5	2
83	YASHWANTH	I12022765	7Y	M	92	28000	12.7	32.1	4	-	25	2	-	3	-
84	GOWTHAM	I12023336	11Y	M	172	24000	19.5	56.7	5	3P&1F	33	2	+	5	3
85	SANGAMITHRA	I12023439	7Y	F	47	33000	12.8	34.7	3	-	22	2	-	6	2
86	RAMYA	I12023678	6Y	F	68	13000	15.1	61.5	3	2 P	27	2	+	5	3
87	AMRITA	I12023917	7Y	F	97	94000	12.6	29.4	2	-	19	1	-	3	-
88	NITESH	I12024682	12Y	M	114	82000	13.0	31.4	3	-	34	2	-	3	-
89	KOWSHIKA	I12024704	6Y	F	46	42000	12.5	29.5	2	-	18	2	-	4	-
90	GOKUL.G	I12024851	8Y	M	122	64000	14.3	49.4	3	2 P	38	2	+	5	3
91	PRIYADARSHNI	I12025058	9Y	F	118	62000	13.4	37.4	3	-	34	2	+	6	2
92	GOKUL	I12025077	10Y	M	155	54000	12.2	33.7	2	-	37	1	-	3	-
93	ARUN	I12025195	14Y	M	102	18000	14.5	44.6	2	2 P	35	1	+	7	3
94	CHIRANJEEV	I12025367	3Y	M	242	88000	13.8	38.4	3	-	29	1	+	4	2
95	HARISH	I12026338	5M	M	56	50000	12.8	36.4	5	-	24	1	+	4	2
96	SUJITHA	I12026385	2Y	F	138	14000	16.6	50.1	4	2 P	38	2	+	6	3
97	THANIKAIVEL	I12026679	10Y	M	74	42000	13.2	34.5	3	-	33	2	-	5	-
98	VIGNESH	I12026558	13Y	M	56	66000	12.8	30.8	4	-	28	2	-	4	-

S NO	NAME		A	S	SG	PL	PT	AP	LS	T	RS	T	C	D	PS
1	SRIMATHI	I11019478	9Y	F	34	86000	13	31.2	3	-	-	2	-	5	-
2	KISHORE	I11019479	1Y	M	35	119000	11.4	29.4	2	-	-	1	-	3	-
3	AJAY KUMAR	I11019630	6Y	M	26	80000	13.8	36	2	-	-	2	-	3	-
4	DURAI	I11019833	8Y	M	22	44000	11.5	30.2	-	-	-	2	-	5	-
5	DHARSHAN	I11020422	7Y	M	24	46000	12.4	32.5	2	-	-	2	-	5	-
6	DHANYA	I11023848	4Y	F	29	57000	12.8	35.1	2	-	-	2	-	5	-
7	HAFRAAN	I11024033	10M	M	37	20000	12.3	42.5	4	-	-	1	-	5	-
8	DEEPA	I11025292	10Y	F	34	58000	14.4	21.9	3	-	-	2	+	7	2
9	SRINIVAS	I11025758	4Y	M	30	91000	11.8	30.8	2	-	-	1	-	6	-
10	MITHUN	I11026389	6Y	M	24	120000	-	-	-	-	-	1	-	5	-
11	KAMAL	I11027096	14Y	M	35	50000	12.4	35.9	2	-	-	2	-	6	-
12	MONIKA	I11027890	14Y	F	24	23000	13.6	44.6	3	-	-	2	-	5	-
13	FAYAZ	I11028483	14Y	M	24	114000	-	-	-	-	-	1	-	6	-
14	DHAKNESHWAR	I11028487	5Y	M	36	23000	14.8	40.1	3	-	-	2	-	6	-
15	KEERTHIKA	I11028503	12Y	F	12	83000	12.7	32.5	-	-	-	1	-	4	-
16	GOWTHAM	I11028504	13Y	M	26	77000	11.9	31.9	-	-	-	2	-	5	-
17	JAMES	I11028721	7Y	M	11	84000	12.7	30.8	-	-	-	2	-	4	-
18	SRI VISHNU	I11033726	4Y	M	28	86000	12.5	33.1	3	-	-	1	-	4	-
19	TAMILARASI	I11034853	9Y	M	25	38000	14.1	38.7	2	-	-	2	-	4	-
20	ASHWIN RAJ	I12010632	3Y	M	31	100000	11.5	34.9	-	-	-	2	-	5	-

S NO	NAME		A	S	SG	LP	PT	AP	LS	T	R	T	C	D	PS
21	BHUVNESHWRI	I12011129	7Y	F	34	67000	11.8	29.4	3	-	-	2	-	5	-
22	GOKUL.R	I12014624	7Y	M	32	110000	12.4	30.5	2	-	-	2	-	3	-
23	SRIVARSHAN	I12015742	12Y	M	18	64000	11.9	30	2	-	-	2	-	5	-
24	DEVASH.S	I12015815	11Y	M	38	96000	13	29.6	4	-	-	2	-	4	-
25	KAVIYA	I12016246	3Y	F	27	77000	12.9	26.4	3	-	-	2	-	5	-
26	ASHOK KUMAR	I12016550	14Y	M	30	38000	13	29.6	3	-	-	2	-	4	-
27	GLADIAS SHERIN	I12016715	12Y	F	23	35000	12.6	28.4	3	-	-	2	-	4	-
28	ROHIT		4Y	M	30	20000	11.8	29.4	4	-	-	2	-	5	-
29	PRABHAKARAN	I12020220	12Y	M	28	30000	13.4	30.7	4	-	-	2	-	5	-
30	MITHUN	I12020354	12Y	M	15	113000	-	-	2	-	-	2	-	4	-
31	RAJESH.R	I12022249	14Y	M	26	14000	13	29.6	-	-	-	2	-	8	-
32	SAJITH	I12022284	6Y	M	31	75000	11.8	30.2	-	-	-	2	-	5	-
33	THIRUPATHI	I12022392	14Y	M	16	145000	-	-	-	-	-	2	-	4	-
34	MUKESH	I12022588	11Y	M	11	136000	-	-	-	-	-	2	-	7	-
35	BHARANIDHRAN	I12022705	5Y	M	25	82000	-	-	4	-	-	1	-	3	-
36	RIFAYA	I12022945	1Y	F	25	16000			5	-	-	1	-	7	-
37	ABILASH	I12022952	13Y	M	21	135000	-	-	2	-	-	2	-	3	-
38	SANTHOSH	I12023317	14Y	M	31	25000	12.3	33.2	4	-	-	2	+	5	2